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Pan-European investigation of neonatal and paediatric parenteral nutrition

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PAN-EUROPEAN INVESTIGATION OF NEONATAL AND PAEDIATRIC PARENTERAL NUTRITION

submitted by Bettina Ursula Klüttgens

for the degree of PhD for the University of Bath

2003

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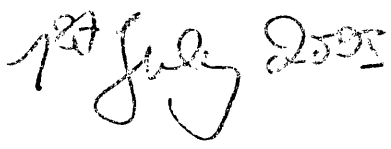
Signed  Date 

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Pan-European investigation of neonatal and paediatric parenteral nutrition

Summary

Parenteral nutrition (PN) support is well established for neonatal and paediatric patients. This form of nutrition support is however highly invasive and therefore not without risk. Multidisciplinary approach is essential for the successful management of parenteral nutrition in hospitals and health-care professionals can refer to international recommendations for guidance.
Review of the literature established that little is known about how well guidelines are translated into practice and how hospitals throughout Europe actually manage PN for neonatal and paediatric patients.
Knowledge of current practice is important for evaluations of quality of care, and in order to identify areas for future improvements.

This research project investigated prescribing, administration, and manufacturing practice of parenteral nutrition for paediatric and neonatal patients in five European countries. Practice was found to be diverse, especially with regard to the involvement of pharmacy compounding units. Several hospitals used internally manufactured standardised parenteral nutrition for neonates.

Prescribing practice for neonates was subsequently studied in more detail in sixteen hospitals across Europe. Prescribing practice was analysed for neonates of differing weight, the influence of enteral feeding on parenteral nutrition prescription was investigated, and other clinical factors were studied. Intake of nutrients, especially amino acids, was found to be below current recommendations, and on a significant number of days less than eighty percent of prescribed nutrition was administered.

The method of administration of lipid emulsions remains controversial in the literature. One aspect of pharmaceutical quality control, lipid peroxidation, was therefore investigated in more detail, in order to inform the discussion regarding administration of lipids as separate infusions, or in combination with other parenteral nutrition components.

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I would also like to acknowledge the contribution of a European discussion group, which was funded and organised by Baxter Healthcare. Members of this group provided stimulating discussions and supported the interpretation of this work. Some members also encouraged their hospitals to participate in the neonatal nutrition study, and I would especially like to thank them for facilitating international data collection.

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I thank the Pharmaceutical Technology group at the University of Bath for making me their honorary member. One of the figures in this document is dedicated to them – they know which one.

I thank my parents for teaching me about the importance of education, for enabling me to study in Germany, and for making my initial visit to England possible – if only they had known that I would not be returning…

Most of all, I thank Andy for his understanding, advice, and support throughout the project.

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List of abbreviations

ASPEN	American Society for Parenteral and Enteral Nutrition
BAPEN	British Association for Parenteral and Enteral Nutrition
BANS	British Artificial Nutrition Survey
BPC	British Pharmaceutical Conference
CV	Coefficient of Variance
DHA	Dehydro-Ascorbic Acid
EN	Enteral Nutrition
ESPEN	European Society for Parenteral and Enteral Nutrition
EVA	Ethyl-Vinyl-Acetate
FOX	Ferrous Oxidation – Xylenol Orange
GH	General District Hospital (UK)
GSH	Glutathione
GSSH	Glutathione (oxidised form)
HPLC	High Performance Liquid Chromatography
ITH	International Teaching (University) Hospital
LCT	Long Chain Triglyceride
LPO	Lipid Hydrogen Peroxides
MCT	Medium Chain Triglyceride
MDA	Malondialdehyde
NEC	Necrotizing Enterocolitis
NHS	National Health Service (UK)
PEG	Percutaneous endoscopic gastrostomy
PN	Parenteral Nutrition
ROS	Reactive Oxygen Species
SD	Standard Deviation
StSol	Standard PN Solutions
TBH	*Tert*-Butyl Hydroperoxide
TH	Teaching (University) Hospital (UK)
TNA	Total Nutrients Admixture
TPP	Triphenylphosphine
USA	United States of America

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1. Literature review

1.1. Definition of parenteral nutrition

Parenteral nutrition (PN) has been defined by the American Society for Parenteral and Enteral Nutrition (ASPEN) as 'nutrients provided intravenously'.[1]

1.2. Historical aspects of parenteral nutrition

The earliest experimental attempts of intravenous nutrient administration occurred in the 1600s, when milk and wine were administered to dogs.[2] In the 1800s, intravenous saline was used to treat cholera, and, by 1930, glucose 5% was used to maintain fluid balance intravenously.[3] Glucose administration was limited due to the susceptibility of peripheral veins to hyperosmolar solutions.[3] The first attempts to provide protein intravenously occurred in Sweden during the 1940s in the form of protein hydrolysate.[4] The main drawbacks of this practice were incidences of severe allergic reaction. Additionally it was difficult to provide adequate calories to utilize the protein because glucose administration was restricted.[5] In order to increase calories provided without having to increase glucose concentrations, alcohol and lipid emulsion were used. Alcohol proved to have severe side effects, but lipid emulsions, first from cottonseed oil and later from soybean oil, were well tolerated.[4] A major breakthrough was the introduction of central venous catheters in 1967, which allowed the infusion of hyperosmolar fluids.[3]

Since then, crystalline amino acid solutions have been developed for adult and paediatric use, and several types of lipid emulsions have become commercially available.[6-8]

Paediatric patients have been the focus of nutrition support, due to their vulnerability to malnutrition, and one of the first reports of successful continuous intravenous feeding of premature neonates dates back to 1975.[9]

1.3. Indications for parenteral nutrition

1.3.1. Neonates

PN is only indicated if oral or enteral nutrition is not sufficiently digested or absorbed, for example in premature neonates, whose gastrointestinal tract is not fully developed.[10] Other indications include congenital malformations such as gastroschisis and omphalocele. These are abnormalities in the formation of the abdominal wall that require PN administration until surgical corrections have been undertaken.[3] Another important indication for PN in neonates is necrotizing enterocolitis (NEC).[3] NEC can develop in the event of an ischemic or toxic insult to the bowel mucosa. In neonates, this can be due to perinatal hypoxia. Breast milk has been shown to reduce the incident of NEC, but the role enteral feeding plays in the prevention of NEC is still unclear.[11] Indications for PN not related to the gastrointestinal tract include cardiac anomalies, such as ductus arteriosus, and respiratory insufficiencies, such as respiratory distress syndrome.[3]

1.3.2. Infants and children

Infants and children represent a very diverse group of patients to receive PN. Indications include gastrointestinal (Table 1.1) or hypermetabolic (Table 1.2) conditions.[12]

Gastrointestinal conditions	
Surgical	Short Bowel Syndrome
	Fistulas
Inflammatory	Necrotizing Enterocolitis
	Inflammatory Bowel Disease
	Acute Pancreatitis
Neuromuscular	Pseudo-obstruction

Table 1.1: Indications for PN in children (gastrointestinal)

Hypermetabolic conditions	
Critical illness	Sepsis
	Burns
	Trauma
	Organ failure
Wasting syndrome	Malignancies
	AIDS
Metabolic disease	Cystic fibrosis

Table 1.2: Indication for PN in children (hypermetabolic)

In some cases, if a large part of the bowel has been surgically removed, long-term PN, which can be administered at home, is required.[13,14]

In recent years, data have been published about the role of both parenteral and enteral nutritional support in children with malignancies.[15] In 1998, Andrassy and colleagues stated that starvation has no role in the treatment of the paediatric cancer patient and that malnutrition should be prevented or treated.[16]

1.4. Nutritional requirements of neonates and children

1.4.1. Neonates

Premature neonates (born before 38 weeks of gestation) have low fat and carbohydrate stores, elevated metabolic rates, and immature gastrointestinal tracts.[17] They therefore require special attention with regard to nutritional support with the aim to achieve growth rates matching those *in utero*.[1]

Recent ASPEN guidelines recommend the following PN provision to stable preterm infants:[1] glucose and amino acids should be started on the first day of life in infants weighing less than 1500 g at birth; glucose should be advanced as tolerated up to 10 to 13 mg/kg/min (equivalent to 14.4 to 18.7 g/kg/day); amino acids should be given at rates of 1 to 1.5 g/kg/day in the first weeks of life, but should be increased to 3.5 to 3.85 g/kg/day for stable infants; total calorie intake should be 100-120 kcal/kg/day in stable infants; lipids should be commenced within the first three days of life, then advanced up to 3g/kg/day.

The guidelines also highlight the fact that enteral feeding should be administered in parallel to PN if at all possible, even if only very small amounts can be given. This recommendation was made because it had been shown that enteral feeding promotes gut maturation and increases feeding tolerance.

Recommended intake of sodium, potassium, and chloride is 2 to 3 mmol/kg/day, but should be subject to continuous evaluation.[3] Recommended intake of other minerals includes 60 to 90 mg/kg/day of calcium, 48 to 68 mg/kg/day of magnesium, and 48 to 68 mg/kg/day of phosphorous, although concentrations of these minerals sometimes have to be restricted due to stability limitations.[18,19]

Vitamins and trace elements form an important part of PN support.[20] These micronutrients are available in the form of commercial micronutrient admixtures (details are shown in section 1.10.1 of this thesis).[3] In some instances trace elements might have to be discontinued, for example copper and manganese in patients exhibiting cholestatic jaundice.[3]

1.4.2. Infants and children

Children require nutrients not only for maintenance of metabolism, but also for growth, and requirements change considerably with age.[3] Estimated energy needs are summarised in Table 1.3.[3]

Age (years)	Daily energy requirements (kcal/kg)
0-1	90-120
1-7	75-90
7-12	60-75
12-18	30-60
>18	25-30

Table 1.3: Estimated energy needs in children

Typical fluid requirement in infants and children are shown in Table 1.4.[3]

Body weight (kg)	Daily fluid requirements
1-10	100 mL/kg
11-20	1000 mL + 50 mL/kg for each kg > 10 kg
>20	1500 mL + 20 mL/kg for each kg > 20 kg

Table 1.4: Typical fluid requirements in infants and children

The following recommendations have been made with regard to nutritional intake in paediatric patients:[1]

a) Protein requirements decrease from 3-4 g/kg/day in premature infants to 1.0-1.2 g/kg/day in children aged one to ten years. Male adolescents require 0.9 g/kg/day; female adolescents require 0.8 g/kg/day.

b) Carbohydrates should make up 40-50% of caloric intake in infants and children.

c) Infants and young children should have unrestricted lipid intake; older children should limit lipid intake to 30% of total energy.

d) Micronutrients should be components of all PN solutions and enteral nutrition formulas, and blood levels of micronutrients should be monitored periodically.

e) Surgical infants do not require a substantial increase in energy provision, unlike adult surgical patients.

1.5. Nutrients and their intravenous application

1.5.1. Amino acids

Proteins are the dietary source of amino acids. Proteins are required as catalysts and enzymes for metabolic reactions, as hormones, and as structural components of cells.[3] In an oral diet, indigested protein is denatured in the stomach and then hydrolysed, first by pepsin into small fragments, and then by carboxypeptidase into amino acids. Amino acids are then absorbed in the small intestine by active transport.[21]

Nine amino acids are essential in humans: thryptophan, threonine, isoleucin, lysine, valine, leucine, methionine, histidine and phenylalanine.[3] Other amino acids might become essential in certain conditions, such as prematurity.[17] Cysteine and tyrosine for example are considered essential in neonates and young infants because of the immaturity of enzyme activities involved in their synthesis.[22]

The amino acid glutamine (Figure 1.1) has received particular attention in the literature.[23,24] Glutamine can be synthesised from glutamic acid and ammonia under normal circumstances, but it has been shown that glutamine can be deficient in prematurity and in hypermetabolic conditions.[25] Glutamine plays a fundamental role in the oxidative defence in the form of glutathione peroxidase;[26] it is therefore important that sufficient levels of this amino acid are maintained.

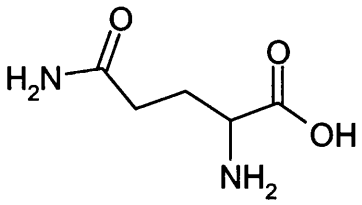

Figure 1.1: Chemical structure of glutamine

Glutamine dissolves poorly in water and is highly unstable.[27] In recent years, products have been developed that allow intravenous administration of glutamine as alanyl-glutamine. This dipeptide is highly soluble and stable in aqueous solutions.[28]

Amin and colleagues investigated arginine in preventing necrotizing enterocolitis (NEC) in a double blind placebo controlled, randomised trial. The researchers found that this amino acid provided significant levels of protection from NEC.[29]

Branched-chain amino acids have been investigated with regard to the prevention of gut atrophy in rats.[30] Branched-chain amino acid metabolism is directly related to glutamine metabolism and can therefore potentially have similar benefits as glutamine.

1.5.2. Carbohydrates

Glucose is the most commonly used carbohydrate for intravenous infusions.[3] Although glucose is not an essential nutrient (it can be synthesized from pyruvate and lactate), it is an important source of energy and thus able to spare proteins from being used as a source of energy.[3] Intravenously infused glucose can be readily used and excess can be stored as fat.[3] Administration of intravenous glucose can cause hyperglycaemia, especially in neonates where insulin production can be insufficient. One way of avoiding hyperglycaemia is to reduce the infusion rate of glucose.[31] However, this will inevitably lead to an insufficient amount of calories provided. It has been suggested that therapeutic concomitant infusion of insulin in neonates receiving parenteral nutrition (PN) can enable continuous provision of glucose and thereby improve nutritional outcome.[32] Glucose contributes substantially to the overall osmolarity of PN solutions. To avoid irritation of peripheral veins, solutions with an osmolarity greater than 900 mOsm/L should be administered via a central vein.[3]

1.5.3. Lipids

Lipids form an important part of nutrition because they provide high-density calories and essential fatty acids.[3] Essential fatty acids, which include linoleic acid (C 18:2 ω-6) and α-linolenic acid (C 18:3 ω-3), play a vital role in the synthesis of prostaglandins, leucotrienes, and thromboxanes.[27] In an oral diet, lipids are absorbed into epithelial cells in the lower gastrointestinal tract, complexed with protein and phospholipids to form chylomicrons, and released into the lymphatic system. They are then discharged into the venous blood at the thoracic duct.[21] Several lipid emulsions are commercially available, including soybean oil, olive oil, structured lipids, and mixtures of medium-chain-triglycerides (MCT) and long-chain-triglycerides (LCT).[7,33,34] New lipid emulsions for intravenous use are being researched and developed with the aim to provide emulsions, which not only provide high caloric nutrition and fatty acids, but also have the potential to modulate immune function.[35] An intravenous application of fish oil, which is particularly rich in ω-3 fatty acids, has also been studied.[34]

Rubin and colleagues investigated the importance of the ratio of medium-chain-triglycerides (MCT) and long-chain-triglycerides (LCT) in parenteral lipid formulations.[33] LCT fatty acids have a chain length of 16-20 carbon atoms; while MCT have 8-12 carbon atoms. They each have different physiological properties with regard to their solubility in plasma and affinity to albumin, and a mixture of both is considered preferable. Rubin and colleagues concluded that MCT fatty acids were safe for use in PN, and that MCT was preferable in hyperbilirubinemia.[33]

Structured lipids are triglycerides that have medium-chain and long-chain fatty acids on one backbone of glycerol, and it has been hypothesised that such emulsions might offer protection from liver dysfunction associated with PN (see also 1.7.2).[36]

1.5.4. Vitamins and trace elements

Vitamins are essential for normal growth and development. They are grouped into water-soluble and lipid-soluble vitamins. Lipid-soluble vitamins are E (tocopherol), A (retinol), D (ergocalciferol/ cholecalciferol), and K (phylloquinone/ menaquinone).[3]

Tocopherols naturally occur in the form of various isomers: alpha, beta, gamma, and delta tocopherol. Alpha tocopherol is the biologically most active isomer.

Lipid soluble vitamins are important for the following physiological processes: inhibition of lipid peroxidation (E), division of cells (A), homeostasis of calcium and phosphorous (D), and synthesis of coagulation factors (K).[3]

Water-soluble vitamins are the B-group ($B_{1, 2, 6, 12}$, pantothenic acid, nicotinamide), vitamin C, folic acid, and biotin. These vitamins form part of enzymes in many physiologically important pathways.[3] Vitamin C is required for synthesis of collagen, absorption of iron, hydroxylation of cholesterol for its excretion in bile acids, and reductive protection of folic acid and vitamin E.[3]

Recent American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines state that vitamins and trace elements should be added to all PN solutions.[1]

1.5.5. Fluids and electrolytes

Fluid and electrolyte management during PN requires continuous evaluation.[3] In particular, premature neonates require close monitoring. These patients have underdeveloped renal and hormonal function, which can affect fluid, sodium and potassium balance.[3]

Parenteral fluids are slowly introduced in neonates, starting at a rate of 60-100 mL per day depending on gestational age.[3] Sodium and potassium are administered according to blood levels, which should be monitored regularly.[37] Normal blood levels for sodium are 133-146 mmol/L and for potassium 3.2-6.0 mmol/L.[38] Chloride intake should not exceed sodium intake in order to prevent metabolic acidosis, and it has been suggested to replace chloride with acetate as an anionic counter ion if necessary.[39]
Children typically require less fluid per kg body weight than neonates. Normal sodium levels range from 133 to 146 mmol/L, and normal potassium levels range from 3.5 to 5.5 mmol/L.[38]

1.5.6. Minerals

Calcium is one of the body's most abundant ions and is important for neuromuscular and enzymatic functions.[3] The vast majority of calcium in the body is stored in bones and teeth, and its metabolism is carefully regulated by parathyroid hormone, calcitonin, and vitamin D.[40]
Magnesium is crucial for many cell functions, such as myocardial function, central nervous system activity, and the activation of enzymes involved in protein and carbohydrate metabolism.[3]
Phosphorous is a structural component of bones and teeth. It also facilitates nerve and muscle function and acts as an acid-base buffer in the urine.[3] It is added to PN solutions in the form of phosphate.
Due to the physiological importance of minerals, it is essential to include them in PN, especially for paediatric patients.[41] However, their effect on PN stability has been of great concern, especially the precipitation of calcium phosphate in paediatric PN.[18,42-45]
In more recent years, organic phosphates, which can be incorporated in PN in greater concentrations than inorganic phosphates without causing precipitation have been used (see also section 1.8.3).[46]

1.6. Oral and enteral nutrition

Enteral nutrition (EN) is often given concomitant to PN. It has been recommended that EN should be commenced in infants receiving PN as soon as possible, in order to promote normal gut motility and reduce the risk of NEC.[1] EN can be administered via an oro- or naso-enteric tube. These tubes are either placed in the stomach or in the small bowel. For patients on long-term EN, tubes are placed via gastrostomy. Prescribers of EN can choose from a wide range of enteral products that are designed for premature neonates, neonates, infants, patients with fluid restriction and patients with other conditions (details of enteral formulae for neonates are shown in Table 4.2).[3] The use of breast milk, even if administered by tube feeding, has been shown to be advantageous for future developments of infants.[47] In preterm infants, breast milk requires fortification in order to provide sufficient amounts of energy.[3]

1.7. Infectious, metabolic, and mechanical complications

PN is an important, often life-saving, form of nutrition support, but administration of PN is also highly invasive and therefore not without risks.[48] Complications can be related to catheter-induced infections, metabolic disturbances due to the composition of the nutrition solution, or mechanical processes of intravenous administration of PN.[48]

1.7.1. Infectious complications

Microbiological infections related to the use of intravenous catheters can either be local or systemic.[49] Catheter related infections remain an important cause of hospital-acquired infection and result in significant morbidity and mortality.[48] Colomb and colleagues studied the incidence of central venous catheter-related infections in children receiving PN at home.[50] They found that, on average, infections occurred on 2.1 of 1000 days of PN treatment. The incidence was much higher in hospitalised patients (6%). Microorganisms causing catheter related infections originate most commonly from patients' skin, *e.g. staphylococcus* species.[48] Treatment of these infections depends on whether it is local or systemic. Local infections require catheter removal and antiseptic or antibiotic treatment. Systemic infections are sometimes treated with antibiotic without removing the catheter, but catheter removal is usually necessary to clear the infection.[49] ASPEN has published the following guidelines with regard to the prevention of catheter related infections: chlorhexidine should be used to disinfect the

skin before catheter insertion, aseptic techniques should be applied at all times during catheter insertion and care, catheter hub should be disinfected before access, antimicrobial-impregnated catheters should be used in high-risk care settings, and specialised nursing teams should care for venous access devices in patients receiving PN.[1]

1.7.2. Metabolic complications

As nutrients are provided intravenously in PN, the function of the gut in regulating nutrient uptake and excretion is circumvented. This can lead to metabolic disturbances, especially with regard to vitamin and trace element deficiencies, electrolyte abnormalities, acid-base imbalances, and complications related to carbohydrate metabolism.[48] These complications are caused by either excess or inadequate supply of nutrients, and careful consideration of patient requirements and monitoring of biochemical markers can usually prevent these complications.

The most important complication related to PN in paediatrics is hepatobiliary dysfunction, which most commonly manifests itself as cholestasis.[51] This complication is particularly common in long-term PN, and it occurs in 40-60% of children in this group.[51] The aetiology of PN induced cholestasis is mutifactorial and has been linked to recurrent episodes of sepsis, lack of enteral stimulation, and excess lipid intake.[51,52]

1.7.3. Mechanical complications

Intravenous feeding is highly invasive and can cause mechanical injury. Mechanical complications can occur during the placement of catheters, such as venous perforation, myocardial perforation, and pneumothorax.[48]

It has been recommended that the correct placement of central catheters should be verified by X-ray.[1]

The Department of Health in the UK recently conducted a review into the death of four infants. These deaths were related to cardiac tamponade during the placement of central venous catheters into the right atrium.[53] Recommendations in this report state that central venous catheter should not be advanced into the right atrium in neonates.

This recommendation has been, however, controversially discussed, and some still recommend to advance catheters into the right atrium.[Sobotka, 2000 #379]

It has to be pointed out that myocardial perforation is extremely rare, compared to other events, such as line blockage, catheter-related sepsis, and lack of venous access.[3]

1.8. Pharmaceutical quality of parenteral nutrition solutions

PN admixtures are complex chemical and physical entities. The manufacture, storage, and administration of these admixtures require careful consideration of pharmaceutical product quality.[54] Product quality with regard to PN can be classified as microbiological quality, physical and chemical stability.

1.8.1. Microbiological quality

Medicinal products for intravenous use must be sterile in order to prevent the risk of systemic infections. Microbial contamination can occur during the manufacture or administration of PN. Therefore, from a pharmaceutical point of view it is important that PN solutions are compounded under strict aseptic conditions. Ideally, PN would be terminally sterilised.[55]

Macronutrients can be administered intravenously in the form of binary admixtures containing glucose and amino acids. Lipid emulsions can either be provided separately from this binary admixture, or in the form of total nutrient admixtures (TNA). TNA are tertiary admixtures containing glucose, amino acids, and lipids in one single container. The incidence of microbial contaminations in PN solutions has been found to be very low, both in TNA and separate lipid emulsions.[56,57] However, if contamination does occur, the consequences can be fatal. This was the case when PN solutions were contaminated with *Enterobacter cloacae*. These solutions were administered to neonates and resulted in two deaths.[58] It was subsequently established that the drainage system in the PN preparation area had been the source of microbial growth.

Typical contaminants in PN solutions include *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, *Enterobacter cloacae*, and *Candida albicans*.[56]

1.8.2. Chemical stability

Many of the components in PN can undergo degradation or interact with other components during storage. Investigations have particularly focused on the stability of vitamins,[59-64] amino acids, and glucose. The formation of peroxides has also been studied,[65-68] and will be discussed in detail later in this thesis (Chapter 5).

Vitamin C, ascorbic acid, is one of the least stable components of PN. It rapidly undergoes reduction to dehydroascorbic acid in the presence of oxygen (see also Figure 5.1).[69] Dehydroascrobic acid is biologically active, but further degradation can lead to the formation of oxalic acid.[70] Oxalic acid can precipitate with calcium and its generation should be minimised. This can be achieved by using containers that prevent the diffusion of oxygen into the solution.[71]

Other unstable vitamins include thiamine[72] and the photosensitive vitamin A.[73]

Manning and Washington reviewed amino acid stability in detail.[61] One of the least stable amino acids is glutamine. Glutamine can, however, be included in PN solutions in the form of dipeptides.[26]

Glucose can undergo degradation during heat sterilisation and during storage. During exposure to heat, glucose molecules can react to 5- hydroxymethyl-2-furanaldehyde, which can further degrade to levulinic acid and formic acid.[54] Glucose can also undergo complex reactions with amino acids to form N-substituted glucosylamine (Maillard reaction).[61]

Manufacturers of PN components offer stability and compatibility advice for hospital staff involved in the compounding and application of PN. This advice is either derived from extensive stability databases, or rigorous testing of individual formulae.[74]

1.8.3. Physical stability

Precipitation

The most likely source for precipitation in PN solutions is calcium and phosphate (Figure 1.2).[71]

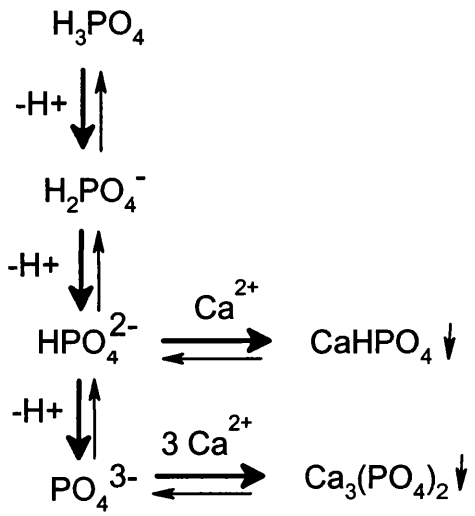

Figure 1.2: Precipitation of calcium and phosphate

Factors influencing the compatibility of calcium and phosphate include pH of final mixture, choice of salts, final concentrations, temperature, order of mixing, and source and concentration of amino acids.[18,75] This problem has now been largely addressed with the introduction of organic phosphates (*e.g.* glucose-1-phosphate and glycerophosphate). Organic phosphates can be included in PN solutions in greater concentrations than inorganic phosphate without the risk of precipitation with calcium.[46] Trace elements can also form insoluble entities in PN admixtures, for example iron phosphate, ferrous citrate, and sodium selenite.[61]

Emulsion stability

Lipids and fatty acid form an important part of PN and are administered to patients intravenously in the form of lipid emulsions.[35] Naturally occurring chylomicrons have a diameter of 0.5-1.0 μm. Particles larger than 6 μm are thought to cause obstruction in pulmonary capillaries, although it has been suggested that particles larger than 7.5 μm in diameter can pass through capillaries due to deformation.[76]

Lipids in commercial products for PN are emulsified by egg phosphatides.[77] The lipid droplet dispersion is maintained by an electrostatic barrier. This barrier derives from a negative surface charge of the emulsifiers phosphate groups. If these stable emulsions are added to the binary PN solutions to form TNA, the physicochemical properties of the emulsion change, and instabilities can occur.[78] The negative surface charge of the lipid droplets can be disturbed by increased concentrations of higher valence cations, such as calcium and magnesium.

Figure 1.3 shows how lipid droplets in a previously stable emulsion (I) can flocculate and rise to the surface (II). If the electrostatic barrier to coalescence is reduced, lipid droplets merge to form larger particle, and eventually the emulsion can crack and show a separate free lipid layer (III).

It has been suggested that the critical diameter for droplets in lipid emulsions for PN is 6 μm, and that no more than 0.4% of droplets should be larger than 5μm for the emulsion to be suitable for administration.[77,78]

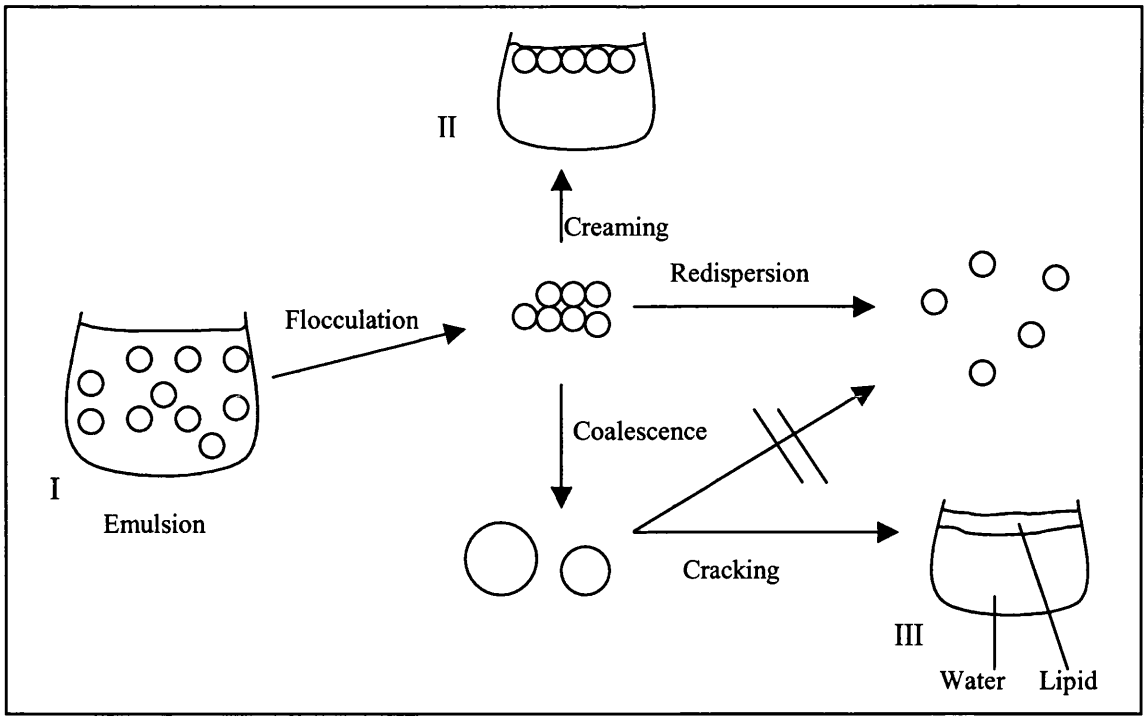

Figure 1.3: Droplet aggregation in lipid emulsions (I = stable; II = creamed; III = cracked emulsion)

1.9. Containers and filters for parenteral nutrition administration

1.9.1. Containers

Traditionally, PN was administered to patients from multiple containers.[79] Amino acids and glucose were available in glass bottles to which other components were added. With the development of ethyl-vinyl-acetate (EVA) containers, it was possible to provide binary admixtures of glucose and amino acids.[80] Currently, various containers are used for PN administration, including EVA and multilayered (oxygen barrier) bags. The layers of oxygen barrier bags typically consist of EVA and ethyl-vinyl-alcohol. Oxygen barrier bags have been shown to reduce oxidation of vitamins during storage.[81]

PN is commercially available in the form of one, two or three compartment bags. One-compartment bags contain either TNA or binary solutions. Compartmentalised bags have the advantage that glucose and amino acids can be terminally sterilised in one container, without the risk of glucose and amino acids undergoing Maillard reaction (as mentioned in section 1.8.2).[82] The seal that separates the components is only broken prior to administration so that an extended shelf life at room temperature can be assigned to these bags. Vitamins and trace elements, however, have to be added aseptically prior to administration.

1.9.2. Filters

In-line filters are used during PN administration to reduce the amount of particles infused. They also reduce the risk of infusing potential microbial contaminants. Due to the large volumes of fluid given when using PN, it is particularly important to minimise the number of particles present in the solution.[83] Filters are also used in the compounding process in order to remove possible particles from rubber bungs or glass vials. The use of administration filters in paediatrics has recently been recommended.[84] Administration filters typically have a pore size of 1.2 μm for lipid emulsions and 0.2 μm for clear solutions. Some have negatively charged surfaces in order to retain endotoxins and can be left *in-situ* for several days. Special paediatric PN filters are also available.

1.10.Commercial products for parenteral nutrition

Commercial products for PN range from component mixutres, such as amino acid solutions, vitamin lyophilisates, and lipid emulsions, to ready-to-use TNA containing glucose, amino acids, lipids, and electrolytes. The list of commercial products presented in this section is by no means complete, but shows details of commonly used products in the UK, especially with regard to paediatric PN.
Information was derived from manufacturers information.

1.10.1. Individual components

Glucose solutions are available in various concentrations ranging from 5-50 g/100 mL and solution volumes ranging from 50 mL to 1000 mL.
The composition of frequently used amino acid solutions is shown in Table 1.4.
Primene and Vaminolact are paediatric formulations; Vamin-9-Glucose is for adult use and also contains glucose.

Amino acids (g/L)	Primene (Baxter Healthcare)	Vaminolact (Fresenius Kabi)	Vamin-9-Glucose (Fresenius Kabi)
L-Alanine	8.0	6.3	3.0
L-Arginine	8.4	4.1	3.3
L-Aspartic acid	6.0	4.1	4.1
L-Cysteine	2.5	1.0	1.4
L-Glutamic acid	10.0	7.1	9.0
Glycine	4.0	2.1	2.1
L-Histidine	3.8	2.1	2.4
L-Isoleucine	6.7	3.1	3.9
L-Leucine	10.0	7.0	5.3
L-Lysine	11.0	5.6	3.9
L-Methionine	2.4	1.3	1.9
L-Phenylalanine	4.2	2.7	5.5
L-Proline	3.0	5.6	8.1
L-Serine	4.0	3.8	7.5
Taurine	0.6	0.3	-
L-Threonine	3.7	3.6	3.0
L-Tryptophan	2.0	1.4	1.0
L-Tyrosine	0.5	0.5	0.5
L-Valine	7.6	3.6	4.3
L-Ornithine	2.5	-	-
Glucose	-	-	100

Table 1.5: Composition of examples of commercially available amino acid solutions for parenteral use

Lipid emulsions typically contain oil, egg phospholipids, glycerol and water. Commercial emulsions differ in their source of oil. Some are derived from plants, such as soybean oil or olive oil. Others are derived from animals, such as fish oil. Still others originate from synthetic oil, such as structured lipids.

An example for a soybean and olive oil based emulsion is ClinOleic from Baxter Healthcare. ClinOleic is available as 20% oil in water emulsion, containing purified olive oil and purified soybean oil (80:20). Other ingredients include: glycerol 2.25 g/100 mL, egg phosphatides 1.2 g/100 mL, and sodium oleate 0.03 g/100 mL.

Lipid emulsions, which contain medium-chain triglycerides (MCT) and long-chain triglycerides (LCT), have been of particular clinical interest.[33,52,85] It was found that MCT/LCT mixtures were more easily oxidised, and were thus more suitable than LCT alone particular in infants with hyperbilirubinemia.[33] The source for MCT is usually

capric acid (40%) and caprylic acid (60%).[86] LCT is typically used in the form of soybean or safflower oil.[7]

The compositions of some vitamin preparations are summarised in Table 1.6. Cernevit should be diluted with 5 mL of water for injection, 0.9% sodium chloride, or 5% glucose. Adults and children over 11 years of age should receive the entire content of one vial. Solivito N should be diluted in 10 mL of Vitlipid N Infant, water for injection, or 5% glucose. Infants and children under 10 years of age should receive 1 mL per kg. Children over the age of 10 years and adults should receive the entire content of one vial. Vitlipid N Infant should be administered at a rate of 1 mL per kg body weight, not exceeding a daily dose of 10 mL in total.

Vitamins	Cernevit (Baxter Healthcare) Power for reconstitution	Solivito N (Fresenius Kabi) Power for reconstitution	Vitlipid N Infant (Fresenius Kabi) In 10 mL
B_1 (Thiamine)	3.5 mg	3.2 mg	-
B_2 (Riboflavin)	4.1 mg	3.6 mg	-
Nicotinamide	46.0 mg	40.0 mg	-
B_6 (Pyridoxine)	4.5 mg	4.0 mg	-
Pantothenic acid	17.3 mg	15.0 mg	-
Biotin	69 µg	60 µg	-
Folic acid	0.4 mg	0.4 mg	-
B_{12} (Cyanocobalamin)	6 µg	5 µg	-
C (Ascorbic acid)	125 mg	100 mg	-
A (Retinol)	3500 IU	-	69 mg
D (Ergocalciferol)	-	-	1.0 mg
D (Cholecalciferol)	220 IU		-
E (α-tocopherol)	10.2 mg	-	0.64 mg
K (Phytomenadione)	-	-	0.02 mg

Table 1.6: Composition of commercial vitamin preparations for parenteral use (IU=International Unit)

Trace elements for paediatric use are available from Fresenius Kabi (Table 1.7). For neonates and paediatric patients, 1 mL of Peditrace should be given. The maximum daily dose is 15 mL.

Trace element (μg/1mL)	Peditrace
Zinc	250
Copper	20
Manganese	1
Selenium	2
Iron	57
Iodine	1

Table 1.7: Composition of Peditrace

1.10.2. Commercially available admixtures

In more recent years, licensed products have been developed that contain several nutrients in one container. Some contain glucose, amino acids, and lipids in one compartment, such as KabiMix from Fresenius Kabi. Advances in container technology mean that PN products are now available which have separate compartments for glucose, amino acids, and lipids. These two- or three- compartment bags do not require refrigeration and can be stored for up to 12 months. The components in each compartment are mixed only prior to administration. An example of a two-compartment product is Clinimix (Baxter Healthcare). Examples of three-compartment bags are Clinomel (Baxter Healthcare), and Kabiven (Fresenius Kabi).

Complete admixtures are now available in various volumes, glucose and amino acids strength, and electrolyte combinations. Unfortunately, micronutrients are not included due to stability limitations. This means that micronutrients have to be added in an aseptic environment to provide complete PN.

These commercial admixtures are currently not licensed for neonates and young children.

1.11. Parenteral nutrition, clinical governance and medicines management

Clinical governance has been defined as 'a framework through which National Health Service (NHS) organisations in the UK are accountable for continuously improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence in clinical care will flourish'.[87]

One aspect of clinical governance is medicines management. This has been defined as 'the entire way that medicines are selected, procured, delivered, prescribed administered, and reviewed to optimise the contribution that medicines make to producing informed and desired outcomes of patient care'.[53]

PN is part of intravenous medical care within hospitals, and it is therefore important to consider the general principles of medicines management applicable to PN.

The 'desired outcome of patient care' with regard to PN, as defined by medicines management, relates to the provision of optimal nutrition support and minimisation of complications, such as metabolic disturbances or sepsis. From a pharmaceutical point of view, it also includes the provision of sterile, stable, and accurately prepared PN solutions. It is also crucial that this high standard of care can be established and maintained in a cost effective way.[53]

Although these definitions and guidelines have been developed by the Department of Health and the Audit Commission in the UK for the management of care in the NHS, general recommendations with regard to medicines management can be extrapolated to an international environment.

The following sections highlight how medicines management is applied to PN, especially with regard to manufacturing and aseptic compounding, standardisation of PN in paediatrics, and multidisciplinary approach to PN.

1.11.1. Manufacturing and quality assurance of parenteral nutrition

Medicines legislation requires licensing of individual medicines (Marketing Authorisation) and also licensing of the manufacturer (Manufacturer License). Whenever possible, licensed medicines should be prescribed over unlicensed products ("specials").[88] It has been recognised that in some cases licensed products cannot meet clinical needs. This is often the case in PN, especially in neonatal and paediatric patients. The production of unlicensed medicines is therefore permitted, provided that

the same quality standards in the manufacturing and quality assurance are met as with licensed medicines. Compounding of PN in hospitals pharmacies follows strict guidelines,[89] and several computer programs and automated systems have been developed and validated to assist with this complex procedure.[90-93]

Unfortunately, due to the complexity of the process of compounding PN solutions, the occurrence of errors is inevitable. Several reports have investigated errors related to intravenous therapy compounding, administration, and compliance with guidelines.[94-96] Implementation of rigorous quality assurance management has been introduced to reduce the frequency of errors.[88,89]

1.11.2. Multidisciplinary approach to parenteral nutrition

In order to provide PN in a safe, nutritionally adequate, and cost effective way, several activities, which involve pharmacists, physicians, dieticians and nurses, have to take place in a coordinated manner. Typically, pharmacists ensure that appropriate products are purchased, that aseptic compounding takes place to the highest standard, and that prescriptions are appropriate, in terms of nutritional adequacy and pharmaceutical stability.

The decisions to start PN and the prescribing of its components are usually undertaken by physicians, although in some hospitals, nutrition support teams have taken over this role.[97-99] Nutrition support teams are interdisciplinary groups of health-care professionals (*e.g.* nurses, physicians, pharmacists, dieticians, biochemists, or others) who meet regularly to decide together which form and amount of nutrition should be provided to patients. Gales and colleagues reviewed comparative trials of nutrition support teams.[100] They found that although these teams were often able to show improved nutrition care in the beginning of their practice, their continuing benefits were less clear. A recently published report by the British Artificial Nutrition Group shows that 38% of 211 hospitals surveyed have nutrition support teams (for enteral and/or parenteral nutrition).[101] However, it is unclear from this report, if neonatal and paediatric PN was included in the teams' responsibilities.

In some hospitals in the UK, pharmacists have taken over the daily prescribing of neonatal and paediatric PN.[88] Interestingly, no information about this practice has been published and it is unclear if training and competency were properly considered.

1.11.3. Standardised parenteral nutrition

The term 'standardisation' has not yet been defined by any of the European or American nutrition societies, yet it has been used inconsistently in publications on both sides of the Atlantic.

For the purpose of this work, standard PN solutions (StSol) have been defined as (right-hand flow in Figure 1.4):

Pre-compounded, batch-manufactured PN solutions
administered to patients according to
individual fluid requirements

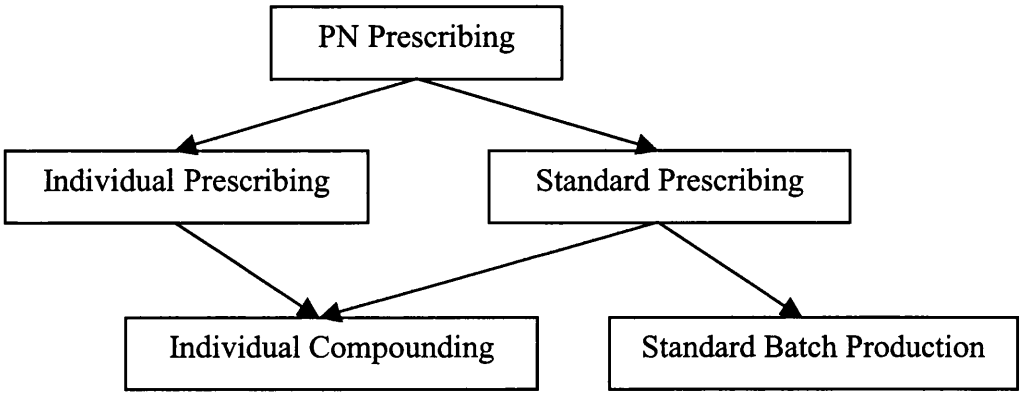

Figure 1.4: Flow chart of standardised prescribing and batch production of PN

The opposite of StSol are customised solutions that are prescribed and compounded according to the individual patient's nutritional and fluid needs (left-hand flow). Several hospitals throughout Europe have published their experiences with StSol in national and international journals.[102-105] Details about hospitals' accounts of the use of StSol will be further explored in section 3.1.1.

Currently published data regarding standardisation of PN exclusively describe accounts of hospitals' experiences. Little information is available regarding nutritional adequacy of standardisation and customisation, economic benefits of one approach versus another, or pharmaceutical safety of PN. More details regarding the use of StSol will be discussed in Chapter 4.

1.11.4. International organisations

Several societies have been formed with the aim to promote specialist nutrition support. These societies specifically focus on the development of guidelines and standards of practice, the promotion of research related to nutrition support, and the provision of a forum of interactions for all professions involved. In the UK, the principle society for enteral and parenteral nutrition is BAPEN (British Associations of Parenteral and Enteral Nutrition). BAPEN was formed by groups representing pharmacists (British Pharmaceutical Nutrition Group), physicians (Clinical Nutrition and Metabolism Group), nurses (National Nurses Nutrition Group), dieticians (Parenteral and Enteral Group of the British Dietetic Association), and patients (Patients on Intravenous and Nasogastric Nutrition Therapy).

On a European level, the principle society is ESPEN (European Society of Parenteral and Enteral Nutrition). In the USA, ASPEN (American Society of Parenteral and Enteral Nutrition) promotes safe and effective nutrition support.

2. Introduction, aims and objectives

2.1. Introduction

Review of the literature has highlighted several aspects of PN that require careful consideration in order to achieve optimal nutrition support:

a) Nutritional assessment / Indications for PN
b) Nutritional requirements and novel components for PN
c) Pharmaceutical quality control / Standardised PN
d) Multidisciplinary approach
e) Cost effectiveness of nutrition support

Appropriate quantities and qualities of nutrition intake have been studied extensively, and new components of parenteral feeding are currently being investigated, such as optimising amino acid intake and modulating immune function by introducing new lipid emulsions. Studies have been undertaken to identify whether different patients have different metabolic requirements. Most recently, aggressive nutrition support has also been explored in neonates to potentially improve nutritional intake. The term 'aggressive nutrition' has been defined as "practice that ranks towards the upper end of the range of established practices, or as practice that goes beyond the established and into untested territory".[31] Aggressive nutrition practice will be discussed in more details in section 4.1.

International organisations have published detailed guidelines regarding nutrition assessment, nutritional requirements in different patients groups, access for the administration of nutrition support, and individuals' responsibilities in multidisciplinary teams.[1,20,106]

Extensive stability studies have been undertaken, especially with regard to lipid emulsions stability, vitamin stability, and precipitation in PN solutions.[81,107-111]

Economic investigations have received little attention, and most reports refer to experiences in one hospital. As a result, these investigations are difficult to extrapolate and generalise.

Little information was found in the literature describing how hospitals in the UK, continental Europe, and USA manage PN support in neonates and children. Knowledge of current practice is vital in order to identify areas for improvement of practice and in order to understand how guidelines and recommendations translate into the care of each patient.

This research project investigated current paediatric PN practice in detail, and focused on the use of StSol in order to identify areas for future improvements. As this project was based at a University, the unique opportunity arose to undertake nutrition practice research that was not based in one hospital. This allowed for an objective evaluation of practice which was not influenced by an investigator's own practice.

In order to gain a broad understanding of clinical and pharmaceutical research methodologies, this project incorporated qualitative research, clinical research, and pharmaceutical method validation and applications.
This project was undertaken on a Pan-European level. For budgetary reasons, the USA and other parts of the world were excluded from the investigations.
Sufficient analysis of the cost effectiveness of PN was found to be lacking in the literature. However, it was beyond the scope of this project to pursue this topic.

2.2. Aims and objectives

The overarching aim of this project was to gain a higher level of understanding of current paediatric and neonatal PN practice in order to inform discussions regarding safety, efficacy and cost effectiveness of this form of nutrition therapy.

The first objective was to establish how neonatal and paediatric PN is managed within hospitals. In order to compare UK practice with other countries, a European wide survey was performed. Information was gathered with regard to prescribing, compounding, and administration practices. The use of StSol was also investigated.

The second objective was to gain a more detailed understanding of nutrition prescribing practice. A study was undertaken comparing PN prescribing practice and nutritional intake in several European countries.

Aims of this part of the project were to compare prescribed and administered PN, to characterise diversity of current prescribing practice, and to compare current PN support with recommendations of nutritional intake.
It was realised that detailed monitoring of all paediatric age groups would not be feasible. It was therefore decided to perform this study in neonates only.

The third objective was to investigate one element of risk management in PN therapy in more detail. Review of the literature had identified that the administration of lipids was discussed controversially, especially with regard to the administration of lipids as TNA or separately from amino acids and glucose solutions. Peroxidation of lipids had previously been investigated, but not with regard to TNA or separate lipid administration. It was therefore decided to quantify lipid peroxidation in different clinically relevant PN solutions and to focus on the way lipids are administered. For this purpose, a novel photometric assay was developed and validated for this application.

A secondary objective throughout the project was to investigate the use of StSol. Many reports had been identified which discuss successful introduction of StSol, in particular for neonatal patients. Each part of the project was designed to gain a better understanding of the use of StSol and to assess the feasibility of introducing StSol. This was achieved by enquiring about the use of StSol and potentially useful compositions of StSol for different age groups; monitoring neonates to facilitate analysis of the diversity of prescribing practice; quantifying lipid peroxides in TNA and lipid emulsions in order to potentially inform decision making with regard to the use of StSol as TNA or separate lipid infusions.

The author of this thesis performed all data collection and analysis. The only exception was that local staff collected data for the neonatal study in international hospitals.
The author of this thesis also executed all laboratory work.
Statistical support was provided by a statistician from the University of Bath and by a statistician from the sponsor.

3. Pan-European survey of paediatric parenteral nutrition practice

3.1. Introduction

3.1.1. Neonatal and paediatric parenteral nutrition practice

The literature was reviewed to assess current practice across Europe in the provision of PN to neonatal and paediatric patients, especially with regard to prescribing, compounding and administration practice. In addition to the literature review, meetings with a European discussion group were attended to explore key issues in paediatric PN in more detail and to discuss potential future developments.

This discussion group was organised by the sponsor with the aim to explore ways in which neonatal and paediatric standardised parenteral nutrition could be introduced in Europe, and what the advantages and disadvantages of such practice would be. The members had previously worked with the sponsor on other nutrition related research projects. Their involvement with the project was related to the following activities: Discussing relevant topics for the European survey, supporting the interpretation of findings from the survey, supporting methodological aspects of the neonatal study (Chapter 4), and discussing findings from the neonatal study. This discussion group also provided suggestions for a standard PN for neonatal patient, as discussed in Chapter 4. The group consisted of paediatricians, neonatologists, and pharmacists from the UK, Germany, Italy, France, Sweden, Belgium, and Finland. Meetings took place on the 3rd July 2000, 10th September 2001, and 6th September 2002.

Three principle stages were identified from the literature with regard to the provision of PN: prescribing, compounding, and administration.

1. Multidisciplinary input into prescribing was explored in the first chapter of this thesis. No publications could be identified in the literature about general prescribing practice in Europe or the involvement of different healthcare professionals.

2. The type of compounding facility employed to provide PN depends on the availability of pharmacy or commercial aseptic services, economical considerations, and availability of trained staff to perform aseptic handling.[88] No matter where PN is compounded or by whom, the most important factors to consider are quality of the final product administered to the patient. The state of current compounding practice

throughout Europe is not known in terms of options for individual compounding or batch preparations of StSol.

3. Various issues arise when considering the administration of PN. The type and location of intravenous catheters is of great importance, and several guidelines and publication discuss this issue.[1,112,113] PN can be given via peripheral or central venous catheters, depending on the length of intravenous feeding and the osmolarity of the PN solution. Long-term PN feeding (*e.g.* more than 10 days) or high osmolarity (*i.e* > 900 mOsm/L) requires the use of a central catheter.[114-116] The location of the tip of central catheters remains controversial (see also section 1.7.3).

Lipids can be administered together with the other nutrients as TNA or administered separately. The main reasons why lipids are typically administered separately are related to the pharmaceutical instability of lipid emulsions and concerns that TNA would provide an excellent growth medium for microbial contaminants.[117,118] It has since been shown that separate lipid emulsions are a better growth medium than TNA.[119]

It is also important to conserve the quality of the PN solution during administration and to ensure that sterile and particle free solutions are administered. Several reports have explored the use of in-line administration filters, and the current recommendation is to always filter both binary solutions and lipid emulsions.[84] As mentioned previously, the protection of bags and administration tubing from light has been suggested in order to protect vitamins and lipids from light induced instabilities and degradation.[120,121] Light protection of bags is relatively easy, and companies supplying PN components often also supply light protective over-wrap bags. However, it is more difficult to protect tubing from light, because nursing staff require easy access to the lines to ensure that they are free of air and free of particles. Current practice in Europe regarding the use of filters and light protection was not known.

Several hospitals in Europe have published their experiences in using StSol. One hospital in London introduced their first standard neonatal bags in 1992.[122]

Another report of StSol usage in Belgium goes back to 1993.[103] StSol were introduced for neonates in intensive care because it was felt that nutritional requirements are relatively stable. The major concern was fluid balance; therefore, it was decided to design four solutions that contain the same amounts of nutrients in four different fluid volumes, allowing the provision of 90 mL/kg/day up to 170 mL/kg/day.[103]

Unfortunately, it was not reported how often each of the solutions was used. A similar approach was adopted in a Spanish hospital where one StSol was used to meet daily

requirements in 100 mL/kg/day. Additionally, this could be diluted to 150 or 190 mL.[102] Interestingly, the 150 mL/kg/day solution was used in 99% of cases. A different system of StSol for neonates was developed in Germany.[105] Two StSol for the first day of PN (5% and 10% glucose) and a 'basic' solution providing all required nutrients in 150 mL/kg/day were available.

In all three cases described, the StSol were used for the majority of neonates. They also reported that compounding errors were reduced and that the standardised approach was more cost-effective. The German hospital had used their system for eight years, and they found that growth and nutritional intake in neonates on standard PN were satisfactory. Despite these positive reports, it has to be pointed out that only hospitals' individual observations were shown, and not results from comparative or randomised trials. Thorough investigations of error reduction, economical benefits, and nutritional adequacy have not been undertaken. One hospital has reported negative outcomes in terms of weight gain and energy intake with StSol after conducting a comparative trial, and they recommend that pharmacist-controlled individual prescribing is advantageous.[123] In a more recent report from the USA, Stettler and colleagues showed that parenteral nutrition support of paediatric patients improved after a standardised system was changed to a customised system.[124] However, improvements were only noted with regard to the delivery of lipids and micronutrients.

The published literature only gives a small account of the current situation in European hospitals. The actual number of hospitals undertaking standardisation of neonatal and paediatric PN is unknown.

Review of the literature revealed that little is known about current European practice in paediatric PN. It is not known how some of the recommendations made in the literature have translated into actual hospital practice. It was therefore decided to undertake a European survey.

3.1.2. Aims and objectives

The overall aims of this survey project were to establish:

a) Current practice of neonatal and paediatric PN treatment in Europe with regard to the prescribing, compounding, and administration of PN

b) Prevalence of StSol usage

c) Composition of StSol in five age/weight groups as considered appropriate by prescribers in the surveyed hospitals

3.2. Methods

3.2.1. Selection of the survey tool

The development of an appropriate tool was required to conduct a survey in Europe. Various techniques can be used to capture information: postal questionnaire survey, telephone survey, or focus groups.[125]

Postal questionnaires have the advantage that a large number of people can be reached and that this technique is relatively cost effective. The disadvantage is that respondents cannot be probed and further explanations cannot be provided. Response rates are also usually lower compared with, for example, telephone surveys.[125]

As the targets were many hospitals all over Europe, which included many different languages, both telephone surveys and focus groups were unsuitable. Focus groups would have provided detailed insight from a limited number of individuals, but would not have been able to capture a large number of hospitals.

It was decided that a postal questionnaire survey would be most suitable for this purpose.

Several stages of development for this questionnaire were identified:

- Exploratory interviews, first in the UK and subsequently in other countries
- Design of questionnaires for the purpose of piloting
- Design and validation of final questionnaires for postal survey.

3.2.2. Selection of hospitals in Europe

Once the decision had been made that a postal questionnaire survey was to be conducted, a list of potential contacts was required. It was not feasible to contact all hospitals in Europe, due to the large numbers. Additionally, sending questionnaires to personal contacts rather than anonymously, can increase response rates.[125] A database was required, which contained names of hospitals and names of healthcare professional, who dealt with neonatal or paediatric parenteral nutrition.

Firstly, international and national specialist nutrition organisations were contacted to find out if such database already exists. Not surprisingly, their responses were negative. Secondly, the commercial sponsor was contacted. They were able to provide a database, which contained the names of physicians and pharmacists in 238 hospitals in the UK, Germany, France, Italy, and Spain. This database was in place for the company's

representatives to maintain contact with customers and non-customers in each country. Due to the fact that this was not purely a customer database, it was felt that, although not an ideal source, this database was suitable to the purpose of this survey.

3.2.3. Questionnaire development – Explorative interviews

After it had been decided whom the questionnaire should be sent to, development of the survey tool commenced.

Firstly, topics of current interest were identified from the literature.

Secondly, these topics were discussed in face-to-face exploratory interviews with pharmacists involved in prescribing and compounding PN in the UK. These interviews were informal, one-to-one discussions. Pharmacists in the Bath and Bristol area were contacted, and three agreed to participate.

3.2.4. Questionnaire development – International interviews

In order to get a better understanding of current topics in the five countries, which had been identified for the survey, further interviews were conducted.

The initial discussions in the UK had assisted with the development of a first questionnaire (Appendix 1), which was used to guide interviews on an international level. Twenty-two interviews were conducted in Germany, France, Italy, Spain, and the UK. Half of interviewees were pharmacists, and half were physicians, and in each case interviewees were nationally recognised experts in the field of neonatal and paediatric PN. Interviews were recorded on voice recorders after obtaining permission from the interviewees.

The objective was to further explore issues identified in the literature, and to discover new aspects that had previously not been considered. An important role of the interviews was also to identify cultural differences between countries and to determine terminology used.

The interviews revealed areas of interest that had previously not been considered. For example, the use of filters and light protection during the administration of PN was important to a number of respondents. Other areas were found to be standard practice in all centres. As an example, the administration of vitamin K to infants was widely practised and therefore not included in the subsequent survey. PN given to patients in their home proved to be a complex legal topic in some countries so these questions were

subsequently removed. Detailed information about the scope of home PN in the UK was available elsewhere.[101]
Because definitions of the role of various professions within the hospital setting differed between countries, this was changed from a closed to an open question in the final questionnaire. The use of computer programs for prescribing and compounding was found to be widespread. Due to the large number of different programs and internally developed systems, it was felt that questions about this subject would not lead to meaningful results.
Most hospitals had different policies for neonatal and paediatric care. In order to appropriately reflect this, questions in the final questionnaire were split into the two patient groups.

One of the objectives of the survey was to investigate the frequency of StSol usage, how they are used, and what the composition of those StSol is. The exploratory questionnaire proved to be too prescriptive to be able to achieve those aims. A more detailed section was subsequently developed for the postal survey.

3.2.5. Questionnaire development – Piloting

By implementing findings from the exploratory interviews, a postal questionnaire was developed for piloting. Native speakers resident at the University of Bath translated into this questionnaire French, German, Italian, and Spanish. Translations were validated by reverse translation process.
In order to validate reliability of some of the crucial questions, the same topic was addressed in two different questions. The question about compounding facilities was addressed in question four ('Is there a unit in your hospital that compounds parenteral nutrition?') and in question fourteen and fifteen ('Is PN ... prepared on the ward? Are ingredients ... added on the ward?'). Information about the source of StSol formulae was addressed in questions nineteen ('Where does the formulation ... come from?') and twenty ('Are commercially available...solutions used...').

Firstly, the questionnaire was discussed with the European discussion group.
Secondly, this questionnaire and a cover letter were sent to four hospitals, which were randomly chosen from the database described above. Participants were not advised that this was a pilot questionnaire, and they were not asked for further comments.

Ten pilot questionnaires were returned (50%). The returned questionnaires were completed satisfactorily and no further changes were made to the questionnaire (Appendix 2).

3.2.6. Final postal survey

The questionnaire was sent to 218 hospitals in Germany, France, Italy, Spain, and the UK (Germany 45, France 43, Italy 55, Spain 31, and the UK 43). Table 3.1 shows the proportion of healthcare professional was contacted in each country.

	Physicians	Pharmacists
UK	3	41
Germany	44	1
France	23	20
Italy	54	1
Spain	30	1

Table 3.1: Proportion of healthcare professional contacted in each country

Several strategies have been suggested to increase response rates from postal questionnaires, including the length and appearance of questionnaires, nature of return envelopes, conduct of follow-up, and other strategies.[125] These suggestions were implemented as applicable to this survey: participants were guaranteed confidentiality, free return envelopes were included with every questionnaire (freepost reply envelopes in the UK and stamped envelopes for other countries), and participants were promised to be sent a summary of results.

Follow-up was conducted by telephone in Germany, France, and the UK, and by e-mail in Spain and Italy.

The following ethical considerations were made: all participants were informed that a commercial sponsor funded the survey, and all information was kept confidential and in secure facilities.

Results were analysed using SPSS 10.0 for Windows.

3.3. Results

3.3.1. Response rates and demographics of responding hospitals

98 hospitals (45%) responded to the questionnaire. Individual countries' responses were: Germany 20 (44%), France 20 (45%), Italy 16 (29%), Spain 11 (36%), and UK 31 (71%). Proportions of healthcare professional are shown in Figure 3.1.

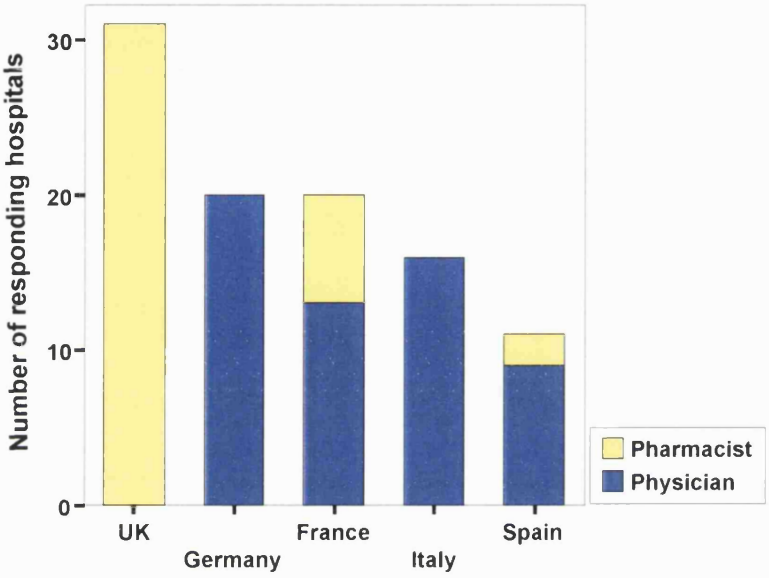

Figure 3.1: Proportion of healthcare professions who responded in each country

Proportions of responses from each country are shown in Figure 3.2.

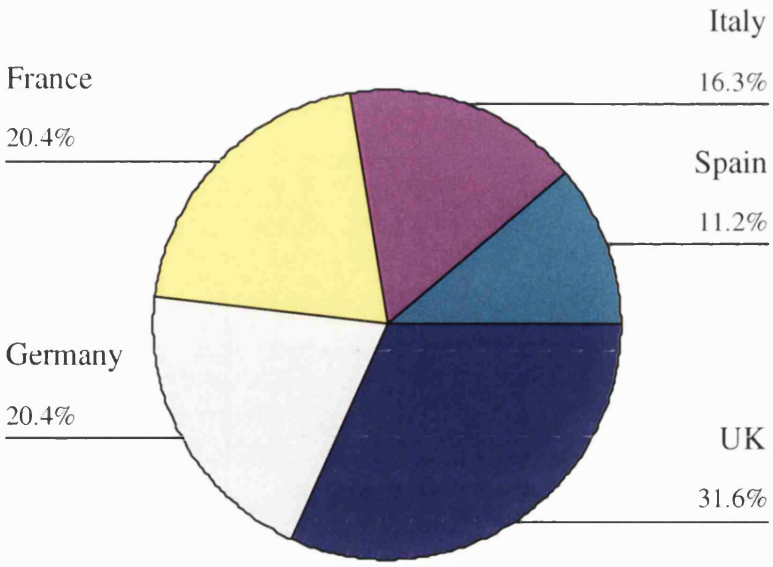

Figure 3.2: Proportions of total responses from each of the five countries (N=98)

Responding hospitals differed greatly in number of neonatal and paediatric beds. Number of neonatal beds (mean ± SD) was 29 ± 17, and number of paediatric beds (mean ± SD) was 98 ± 94. Figure 3.3 shows how many PN infusions were typically administered per day in responding hospitals.

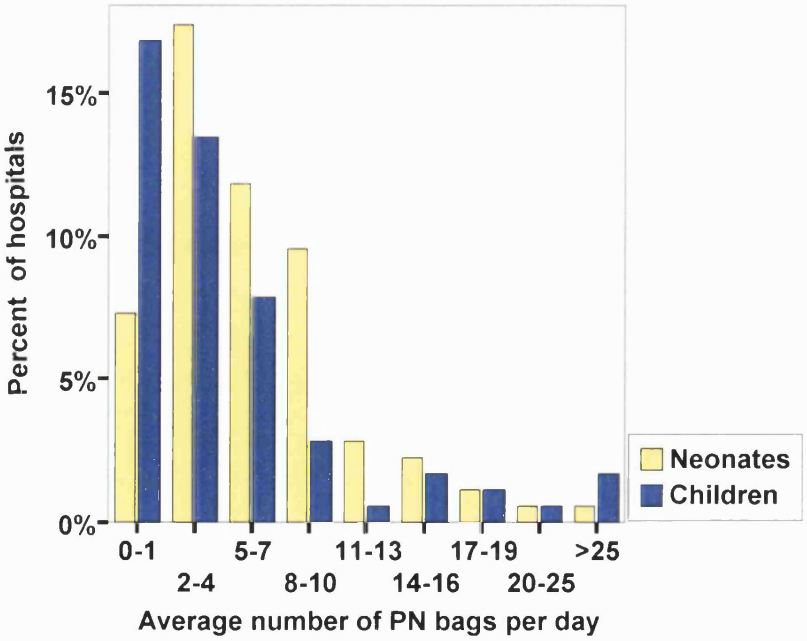

Figure 3.3: Average number of PN bags per day for neonates and children in all hospitals (N=98)

3.3.2. Parenteral nutrition prescribing

PN was prescribed by physicians in 81% (N=79) and by pharmacists in 6% (N=6) of hospitals. In 13% (N=13) of hospitals either physicians or pharmacists prescribed PN. Pharmacist prescribing was found only to occur in the UK.

3.3.3. Parenteral nutrition compounding

There were clear differences in the preparation of PN throughout Europe. Compounding units for aseptic PN preparation were present in 35% of hospitals in Germany and in 40% of hospitals in France. In Italy, these dedicated PN facilities were present in 50% of hospitals, compared to 64% of hospitals in Spain. The largest percentage of hospitals with compounding units was in the UK with 87%.
Overall, 21 hospitals (22%) compounded PN on the ward regularly, 10 (10%) rarely, and 66 never (68%) (No reply from one hospital). Figure 3.4 shows how often additions, such as vitamins, trace elements, electrolytes or drugs were made to the PN bag on the ward.

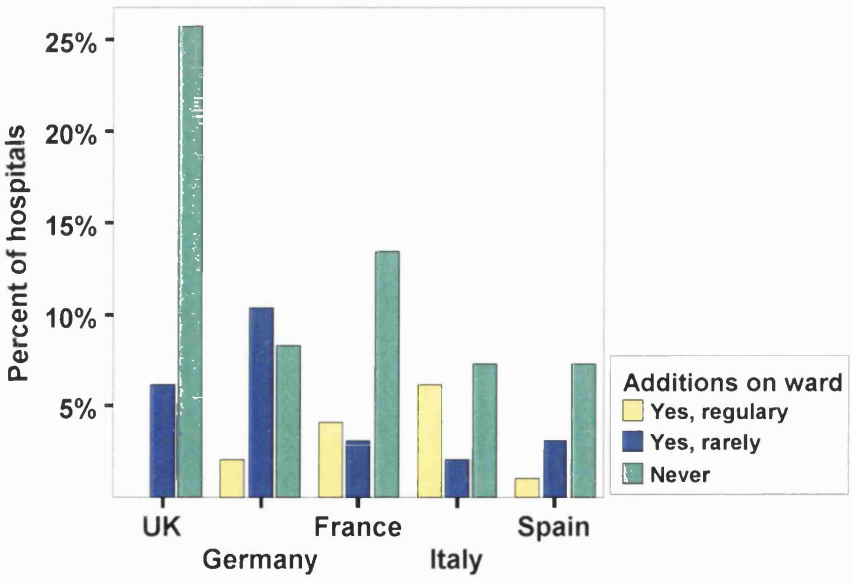

Figure 3.4: Number of hospitals in each country where additions to PN were made on the ward and frequency of additions

3.3.4. Parenteral nutrition practice

Lipids were either administered separately from the binary solutions or in form of TNA. Table 3.2 summarises how often lipids were administered separately to neonates and children in each country. This data was derived from Question 7 in Appendix 2. The following classifications were made: separate lipid emulsion 0% = Never; separate lipid emulsion 100% = always; separate lipid emulsion 1-99% = Sometimes.

In the UK and Germany, lipids were always given separately from the binary solution to neonates. TNA use was more common for neonates in France, Italy, and Spain. For children, there was an increased tendency to give lipids in the form of TNA.

	Lipids administered separately from the binary solution					
	Neonates			Children		
	Always	Sometimes	Never	Always	Sometimes	Never
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
UK	28 (100)	0 (0)	0 (0)	8 (33)	11 (46)	5 (21)
Germany	19 (100)	0 (0)	0 (0)	16 (84)	2 (11)	1 (5)
France	11 (55)	3 (19)	2 (13)	7 (50)	4 (29)	3 (21)
Italy	3 (38)	1 (13)	4 (50)	2 (33)	2 (33)	2 (33)
Spain	6 (60)	2 (20)	2 (20)	3 (33)	1 (11)	5 (56)

Table 3.2: Frequency of separate lipid administration in neonates and children in each country

Vitamins and trace elements were not added to the PN solution every day. Participants were asked to indicate when, after commencement of PN, vitamins and trace elements are usually initiated. They were also asked to state how many days per week micronutrients were provided.

The addition of vitamins to PN for neonates and children is shown for water-soluble vitamins in Figure 3.5 and for lipid-soluble vitamins in Figure 3.6 (error bars represent 95% confidence interval of the mean).

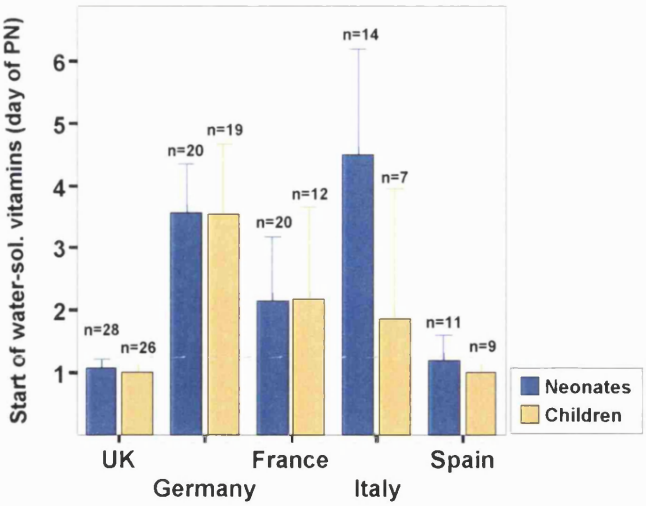

Figure 3.5: Start of water-soluble vitamins for neonates and children in the five countries

In the UK and Spain, water-soluble vitamins were added from the first day of PN. In the other countries, practice was more variable. Hospital in Italy indicated that, on average, water-soluble vitamins were added after four days of PN.

Lipid-soluble vitamins were on average added to PN later than water-soluble vitamins. This was likely to be related to the fact that lipid-soluble vitamins are usually administered concurrently to lipid emulsions. Intravenous lipid administration was, however, commenced later than the administration of binary solution.

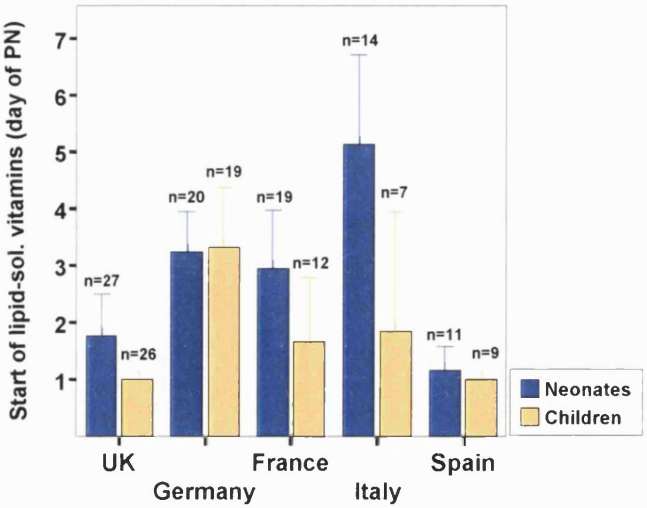

Figure 3.6: Start of lipid-soluble vitamins for neonates and children in the five countries

Vitamins were usually added every day of the week once commenced (83 hospitals (92%)). The remaining hospitals included vitamins between 6 and 3 days per week (7 hospitals (8%)) with no reply from a further 8 hospitals.

Trace elements were commenced much later than vitamins, as shown in Figure 3.7. (error bars represent 95% confidence interval of the mean). One hospital reported to include trace elements after four weeks of PN. Once trace elements were started, they were usually included each day of the week (neonates 94%, children 96%).

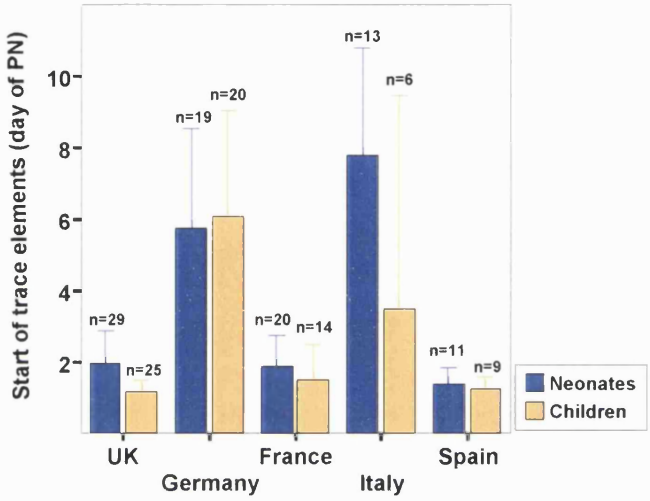

Figure 3.7: Start of trace elements for neonates and children in the five countries

The use of in-line filters has been recommended in order to prevent infusion of microbial contaminants and to reduce the number of particles infused.[84]

Figure 3.8 shows that in-line filters were frequently used in the UK, Germany, and in Spain. In France and Italy, administration filters were not usually applied.

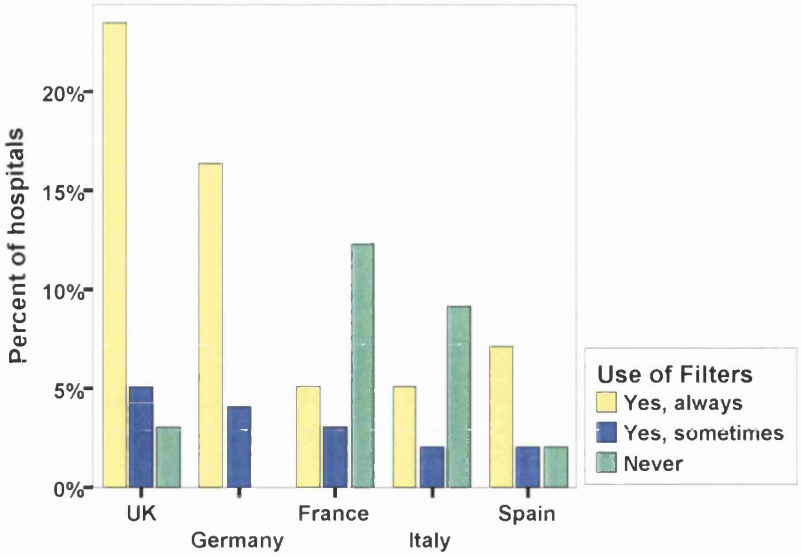

Figure 3.8: Frequency of use of in-line administration filters in each country

Light protection has also been recommended to protect vitamins from light-induced degradation and to reduce peroxidation.[64,126] Table 3.3 summarises how often PN containers and administration tubing were protected from light.

	Light protection during administration					
	Container			Administration tubing		
	Always	Sometimes	Never	Always	Sometimes	Never
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
UK	20 (65)	9 (29)	2 (7)	3 (10)	2 (7)	25 (83)
Germany	6 (30)	8 (40)	6 (30)	3 (17)	11 (61)	4 (22)
France	6 (30)	3 (15)	11 (55)	1 (5)	2 (11)	16 (84)
Italy	10 (63)	2 (13)	4 (25)	5 (31)	4 (25)	7 (44)
Spain	5 (50)	1 (10)	4 (40)	2 (22)	3 (33)	4 (44)

Table 3.3: Frequency of light protection of PN containers and administration tubing during PN administration

3.3.5. Use of standard solutions

Amongst 98 responding hospitals, 79 provided information on the use of StSol. For neonates, 19 hospitals (24%) used StSol. Of those hospitals utilising StSol, 57% used StSol that had been developed and compounded internally, yet some also used StSol in conjunction with other hospitals (21%) or through commercial suppliers (21%). With children, 14 hospitals (18%) reported using StSol. On the other hand, only one hospital had developed internal standard PN specifically for paediatric patients. All other hospitals used products from commercial suppliers.

Open questions were asked to find out more about the reasons why hospitals chose to individualise or standardise PN. Some of the answers are listed below.

Reasons for individualisation:

- 'It is better for the patient to have each bag individualised'
- 'There is a lack of suitable standard products'
- 'Our existing system works well, there is no need to change it'
- 'Our patients are not standard, that is why the nutrition cannot be standard'

Reasons for standardisation:

- 'To allow continuation of supplies during shutdowns'
- 'To start new patients on PN over the weekend'
- 'Better treatment for neonates from day to day'
- 'Better data on stability and sterility'
- 'Our physicians agreed that there was no need to individualise regimens'

Participants of the survey were also invited to supply detailed descriptions about StSol used in their hospital. In regard to internally prepared StSol, five hospitals returned information (two from the UK, two from Germany and one from France), which are summarised in Table 3.4.

In 100 mL	Hospital A	Hospital B	Hospital C	Hospital D	Hospital E
Amino acids (g)	1.7	1.5	1.7	1.3	1.2
Glucose (g)	12.5	10.0	10.0	10.0	11.0
Sodium (mmol)	2.5	3.0	1.5	2.0	1.6
Potassium (mmol)	1.7	2.0	2.0	2.0	1.3

Table 3.4: Neonatal standard solutions used in participating hospitals

Lipids were given separately, and they are not included as part of the standard solutions. One hospital also returned a floppy disc containing an internally developed computer program that facilitated their prescribing of neonatal and paediatric PN.

3.3.6. Suggested standard intake

All participants were invited to suggest potentially suitable StSol based either on their experience with StSol or based on their prescribing practice. Suggestions did not have to be based on current practice, but should have reflected 'ideal' practice. Information was collected for premature neonates, neonates, children <10 kg, children 10-20 kg, and children 21-30 kg body weight. Nutritional information included: volume of PN (mL/kg/day), amino acids (g/kg/day), glucose (g/kg/day), lipids (g/kg/day), sodium (mmol/kg/day), and potassium (mmol/kg/day).

The following figures (Figure 3.9-Figure 3.14) summarise the overall responses in the form of boxplots (the horizontal dotted line represents the median, the boxes represents the quartiles, and the whiskers include all values). Outliers are not shown.

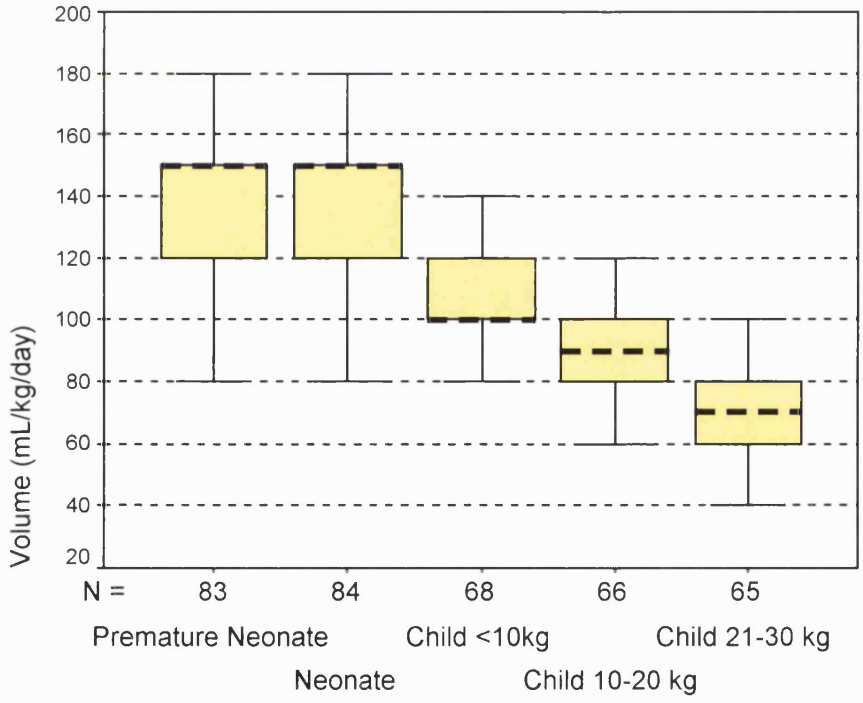

Figure 3.9: Suggested volume (mL/kg/day) for five age/weight groups

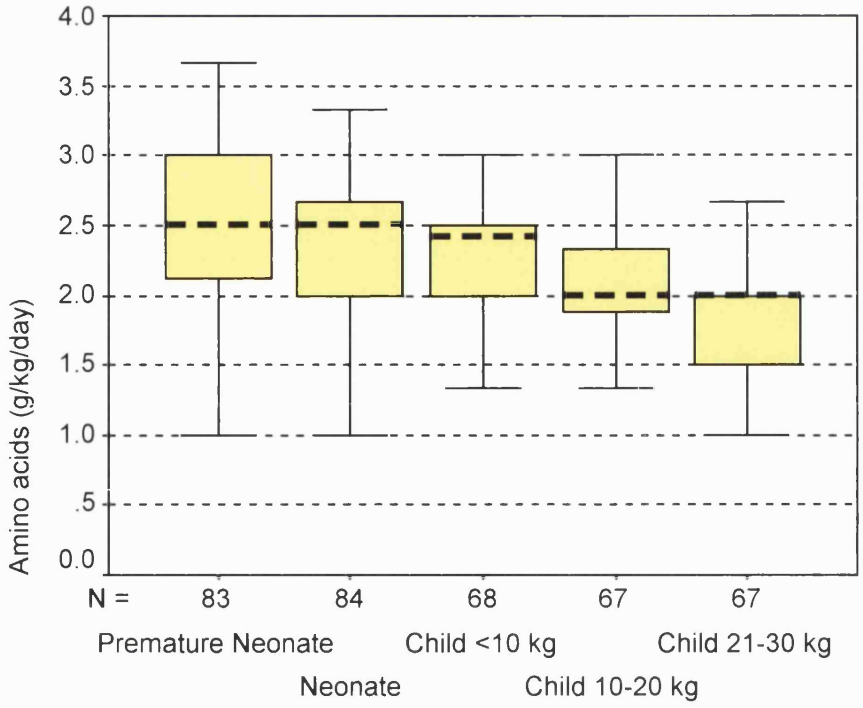

Figure 3.10: Suggested amino acids (g/kg/day) for five age/weight groups

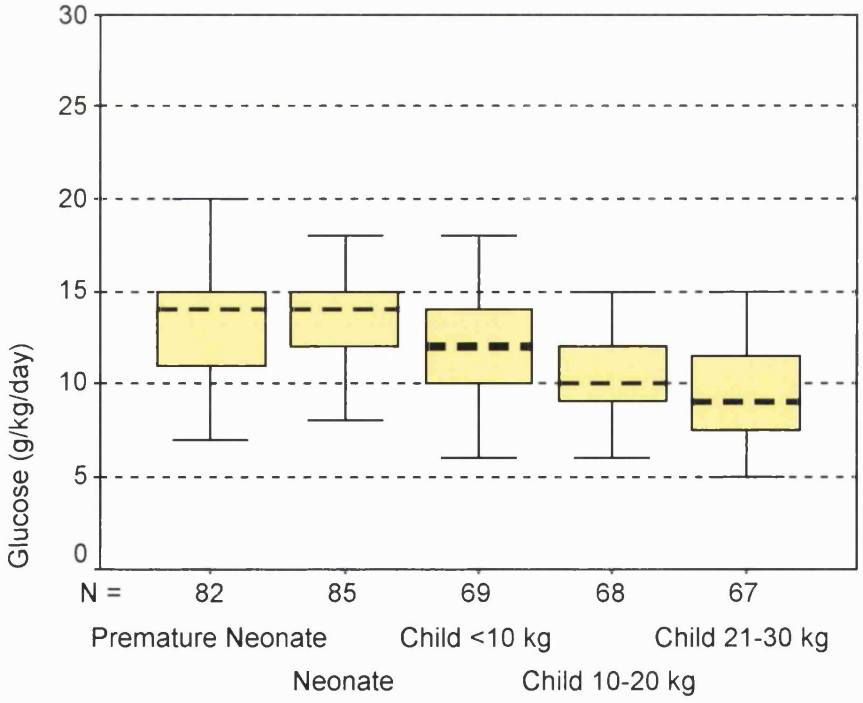

Figure 3.11: Suggested glucose (g/kg/day) for five age/weight groups

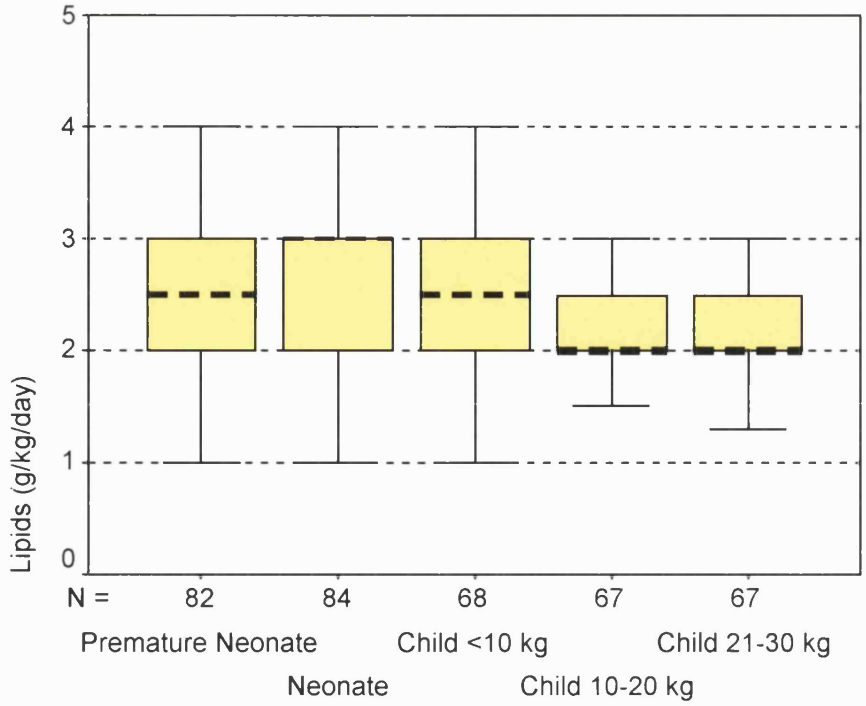

Figure 3.12: Suggested lipids (g/kg/day) for five age/weight groups

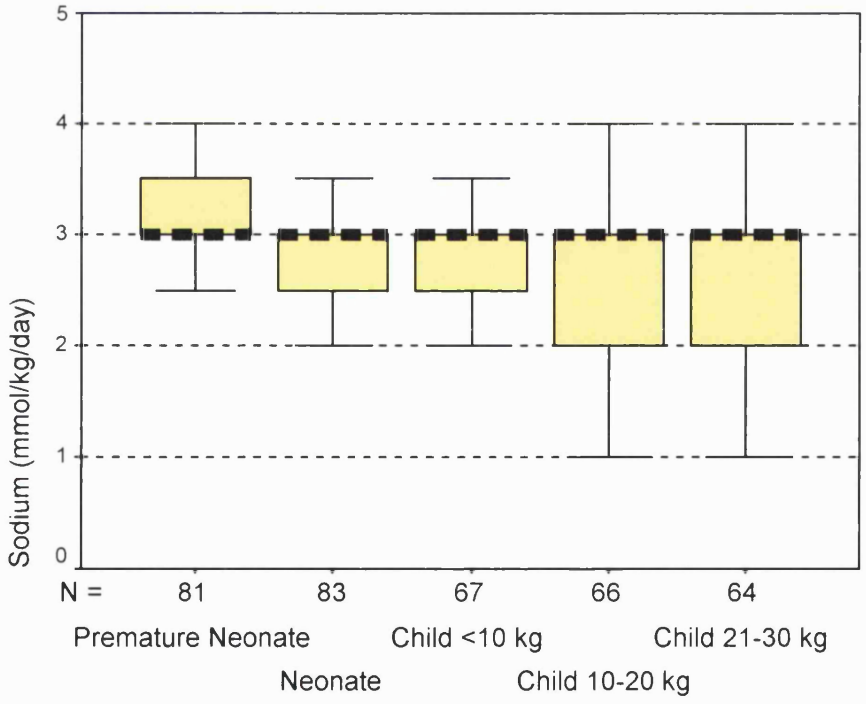

Figure 3.13: Suggested sodium (mmol/kg/day) for five age/weight groups

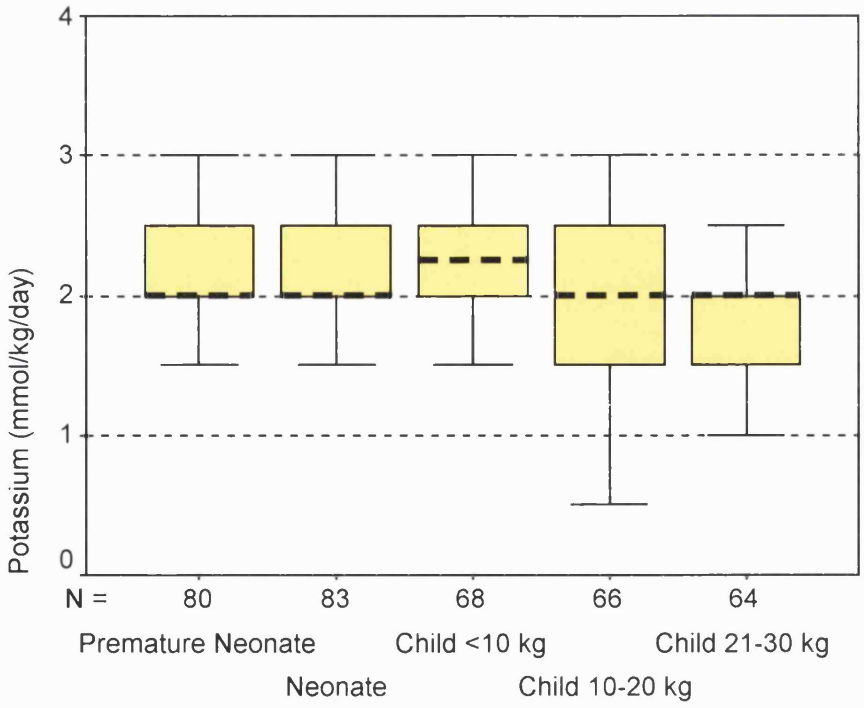

Figure 3.14: Suggested potassium (mmol/kg/day) for five age/weight groups

3.3.7. Grouping responses (Cluster analysis)

Data shown in section 3.3.6 represents responses overall. Due to the diversity of the overall data, responses were grouped according to similarity. This was done using hierarchal cluster analysis. Hierarchal cluster analysis attempts to identify relatively homogeneous groups of cases based on selected characteristics. In this case, the following groups were used: amino acids (g), glucose (g), lipids (g), sodium (mmol), and potassium (mmol). This way it was possible to identify groups of respondents who considered similar StSol suitable for use. Data were standardized by Z score and squared Euclidean distance was used.

Using the suggested PN volume per kg per day, macronutrients and electrolytes were calculated as components per 100 mL (Table 3.5.).

In 100 mL	Premature Neonate	Neonate	Child <10 kg	Child 10-20 kg	Child 21-30 kg
Amino acid (g)	1.8 (1.7-2)	1.8 (1.6-2)	2.1 (1.8-2.6)	2.3 (1.9-2.7)	2.5 (2.2-3.1)
Glucose (g)	9.7 (8-10.6)	10.0 (8.6-11.3)	11.6 (10.0-14)	12 (10.0-14.3)	12.5 (10.0-15.0)
Lipids (g)	1.8 (1.4-2)	2.0 (1.5-2.3)	2.1 (2.0-2.9)	2.5 (2.1-2.9)	2.8 (2.3-3.3)
Sodium (mmol)	1.5 (1.2-1.8)	2.0 (1.9-2.3)	2.5 (2.1-3)	3.0 (2.5-3.8)	3.8 (2.9-4.3)
Potassium (mmol)	1.5 (1.2-1.8)	1.7 (1.3-2.0)	2.0 (1.5-2.5)	2.2 (1.9-2.9)	2.6 (2.0-3.3)

Table 3.5: Median (Interquartile range) for all respondents

Hierarchal cluster analysis was then used to identify sub-populations of PN solutions by taking all components of the suggested StSol into consideration. Several sub-populations were also identified. The two largest clusters (N_1; N_2) in each age group are shown below and include the following number of cases:

Premature neonates: N_1=37 (47%); N_2=17 (22%)

Neonates: N_1=29 (36%); N_2=18 (22%)

Child <10 kg: N_1=30 (47%); N_2=18 (28%)

Child 10-20 kg: N_1=24 (38%); N_2=22 (35%)

Child 21-30 kg: N_1=24 (40%); N_2=11 (18%)

The median and interquartile range for the five components is summarised for the largest cluster in Table 3.6. and then again for the second largest cluster in Table 3.7.

In 100 mL	Premature Neonate	Neonate	Child <10 kg	Child 10-20 kg	Child 21-30 kg
Amino acid (g)	1.8	1.8	1.8	2.5	2.5
	(1.7-2)	(1.6-2)	(1.6-2)	(2.1-2.6)	(2.3-2.9)
Glucose (g)	10.0	10.0	10.0	12	11.7
	(9.3-10)	(10.0-10.0)	(8.3-10.0)	(11.5-12.5)	(11.3-12.5)
Lipids (g)	1.7	2.0	2	2.6	2.7
	(1.3-2)	(1.7-2.3)	(1.7-2.1)	(2.5-3.1)	(2.5-2.9)
Sodium (mmol)	2.0	2.0	2.5	3.3	4.0
	(1.9-2.7)	(2-2.5)	(2.1-3)	(2.9-3.8)	(3.4-4.3)
Potassium (mmol)	1.5	1.3	1.8	2.2	2.6
	(1.3-1.7)	(1.3-1.7)	(1.5-2.1)	(1.9-3.1)	(2.2-2.9)

Table 3.6: Median (Interquartile range) for the largest cluster (N_1) in each age group

In 100 mL	Premature Neonate	Neonate	Child <10 kg	Child 10-20 kg	Child 21-30 kg
Amino acid (g)	1.7	1.7	2.2	2.0	2.5
	(1.5-1.8)	(1.4-1.8)	(2-2.5)	(1.7-2.2)	(2.1-3.1)
Glucose (g)	7.4	8.2	12	9.5	15
	(6.7-8)	(8-8.6)	(11.6-12.5)	(8.1-10)	(14.3-15.6)
Lipid (g)	1.7	2.0	2.3	2.1	2.9
	(1.5-2)	(1.7-2.3)	(2-2.6)	(1.9-2.5)	(2.5-3.1)
Sodium (mmol)	2.0	2.0	2.5	3.0	3.8
	(1.5-2)	(1.8-2.3)	(2.5-3)	(2.5-3.3)	(3.1-3.8)
Potassium (mmol)	1.3	1.3	2.1	2.0	2.9
	(1-1.7)	(1.1-1.8)	(1.9-2.4)	(1.8-2.5)	(2.5-3.3)

Table 3.7: Median (Interquartile range) for the second largest cluster (N_2) in each age group

Further analysis of the cluster groups showed that they could not be grouped by country or size of hospital. This means that each cluster represented respondents from any country and from any type of hospital.

3.4. Discussion – Methodology

Because of the relatively low response rate, results cannot be easily generalised.
One reason for non-responding, as investigated during follow-up, was the low frequency of PN used in some of the hospitals contacted. Unfortunately, follow-up results were not recorded in details. It is therefore not known which percentage of hospitals contacted did not use PN frequently.
Also, since the response rate in the UK was high, the overall results might be biased towards this country.
An improved response rate could have been achieved by:
a) Contacting all centres prior to sending questionnaire, in order to find out if substantial amounts of neonatal and paediatric PN were used and to find out if there was sufficient interest in the subject
b) Employing native speakers to conduct telephone follow-up in Italy and Spain

Another possible interference could have arisen from selective response: hospitals might have been more likely to respond to the questionnaire because they had a special interest in PN and in standard PN. As a result, this could have lead to an overestimation of, for example, the percentage of hospitals using StSol.

The questionnaire used for this survey was also relatively long and complex. Some hospitals who had returned the questionnaire indicated, that they had completed the questionnaire jointly between pharmacists and physicians (for example, if prescribing and compounding was handled completely separately). This had not been envisaged during the development phase and added to the complexity.
During follow-up, some physicians and pharmacists stated that they did not have the time to participate, although they were interested in the subject. This difficulty could have been overcome by splitting the survey into two separate parts. As an example, a postal survey could have been conducted that examined general aspects of PN practice only. Then, a second survey could then have focused on StSol by targeting respondents who had shown an interest in this subject in the first survey.
Despite these concerns, the response rate in this survey was similar to other published European questionnaire surveys where responses ranged from 36% to 42%.[127,128]

Several problems were also detected that can be attributed to the piloting process.

Questions that appeared to perform well during piloting provided inconsistent responses. Responses to the quality control questions, for example, were meaningless, because it became evident that no distinction had been made between *end-control* and *process validation*. Another difficulty, which had not been apparent during interviewing, was related to the specification of manufacturers products used. Different companies in each country supplied products. Consequently, answers to this question were inconsistent and were not presented.

Piloting in five languages and countries proved to be a complex task. Focusing on the UK only for a first study and subsequently expanding the survey overseas might have achieved more successful and complete validation of the survey tool.
The opportunity had been missed to asked hospitals contacted for piloting purpose to comment on the questionnaire. This would have been useful to detect inconsistencies and topics that had been missed during interviewing.
It has to be concluded that postal piloting was unsatisfactory, and that results from this survey have to be interpreted in the light of these shortcomings.
It is also important to highlight the fact that a commercial database was used to contact participants. This was the only identifiable database in Europe, and was not customer database. Nevertheless, results have to be interpreted taking this source of information into consideration.

3.5. Discussion – Survey results

This survey of PN practice in five European countries has investigated prescribing, compounding, and administration of PN. The use of StSol and the composition of StSol in the view of prescribers have also been studied.

The results of this survey show that physicians are mainly responsible for prescribing of PN, although in some hospitals in the UK pharmacists are prescribing. The current legal situation requires the physician to sign PN prescriptions, but some hospitals have introduced policies that allow pharmacists to prescribe PN, or allow nutrition support teams take over a joint prescribing role.[100]

Compounding practice differed greatly throughout Europe. In the UK, most hospitals prepared PN in hospital pharmacy aseptic compounding units, and additions were rarely made to PN bags on the ward (Figure 3.4). Hospitals in Europe that did not have an internal compounding unit either received PN from another hospital, or from commercial contractors, or compounded PN on the ward. In a fifth of surveyed hospitals PN was compounded directly on the ward.

Unfortunately, the opportunity was missed to enquire about hospitals' infection rates as part of the survey. It is therefore not know whether the type of compounding practice had a direct effect on infection rates in each hospital. Discussions about the advantages or disadvantages of compounding PN in pharmacy departments thus remain purely speculative in the context of this survey. Further work is required in order to make recommendations about the optimal location and environment for aseptic compounding of PN.

With regard to the infusion of lipids, results from this survey show that they were mostly given separately, especially in neonatal PN (Table 3.2). Separate infusion of lipids was widespread in neonates in comparison to practice in adults for whom most PN is given as TNA. This may have been surprising, as there is no evidence in the literature that TNA would not be feasible or clinically inappropriate in neonates. Giving lipids as TNA can potentially lead to a more consistent provision of lipids, and doing so might also have economic advantages.[129] Further aspects of separate lipid administration or TNA will be explored in Chapter 5 of this thesis.

Commercially available micronutrient solutions are designed to meet recommended daily intakes. This survey has shown that a substantial number of hospitals did not start micronutrients on the first day of PN, and some did not include it each day of the week

(Figure 3.5-Figure 3.7). Particularly in Germany and Italy, micronutrient addition was frequently delayed until several days after PN commencement.

If micronutrients are not given every day from the first day, a risk of deficiency can occur. During piloting of the questionnaire, it became clear that some hospitals did not include micronutrients due to concerns of their stability or concerns of the effect that micronutrients might have on the stability of other PN components. Regarding the stability of micronutrients in PN, clearer guidance might be required from manufacturers and international organisations, in order to ensure that micronutrients are provided in appropriate concentrations.

Many hospitals filtered PN solutions during administration (Figure 3.8). It has been shown that particles contaminate PN solutions, and recent guidelines have highlighted the importance of filtration of all PN solutions.[17,130]

PN bags were often light protected, but light protection of the administration tubing is currently rare (Table 3.3). This is possibly due to a lack of suitable or affordable materials. Light, especially phototherapy light, can affect the stability of PN is two ways. Light sensitive vitamins are more likely to degrade, and lipid peroxidation is potentially increased.[81,126] More research is needed to show clear benefits of light protection, especially the importance of protecting the administration tubing from light. This topic was further explored as described in chapter five of this thesis.

One of the objectives of this survey was to find out more about current practice with regard to the use of StSol. The results show that StSol had been mainly developed for neonatal patients. Five hospitals have returned information with the questionnaire about the exact composition of their neonatal StSol. The solutions shown in Table 3.4 are comparable to some of the StSol described in the literature.[105] If these solutions were administered at a rate of 150 mL/kg/day, between 1.8 and 2.6 g/kg/day amino acids, then 15 and 18.8 g/kg/day glucose would be provided. Current recommendations of amino acids intake are 3.5-3.85g/kg/day for premature neonates and 2-3 g/kg/day for term neonates.[1] StSol used in some of the surveyed hospitals might provide insufficient amounts of amino acids, especially if used for premature infants.

The second part of the questionnaire asked participants to suggest StSol that they felt would be suitable to use in five age/weight groups. The overall data summarised in Figure 3.9-Figure 3.14 shows that standard concentrations fell steadily with increasing maturity and weight. Only sodium and potassium levels are suggested to remain at approximately 3 and 2 mmol/kg/day respectively. The large variability, especially in terms of proposed amounts fluids and amino acids, suggests that current practice and the

perception of best PN practice is diverse across Europe. Another reason for variability might have been that different hospitals treat different patient populations. This factor was, however, not investigated.

Overall results (Table 3.5) showed a steady increase in all components of PN from premature neonates to older children and interquartile ranges showed that responses were very variable. As a result, cluster analysis was employed to identify homogenous groups of respondents, based on similar responses to all five PN components.

Table 3.6 shows that suggested concentrations of nutrients for premature neonates and term neonates in the largest cluster differed only slightly. Table 3.7 however, shows that a lower glucose concentration might be required in some patients, and this is an approach already used in some hospitals for very premature neonates.[105] Recommended amino acids intake differs for premature and term neonates as described above,[1] but this was not reflected in the results of this survey.

In the three groups of children, concentrations of all components increased steadily, with the exception of sodium. Cluster analysis discriminates two different groups of responses with regard to the glucose concentration, especially for older children where suggestions vary between 11.7% and 15% glucose.

These results have revealed the diversity of current practice, and have highlighted the fact that more guidance is needed regarding controversial issues. Importantly, the use of StSol requires further investigation and guidance.

4. Pan-European study of neonatal nutrition prescribing practice and nutritional intake

4.1. Introduction

4.1.1. Neonatal enteral and parenteral nutrition

Neonates require special nutritional support if born prematurely (before 38 weeks of gestation) or if satisfactory nutrient intake cannot be achieved by oral feeding.[131] The natural food for neonates is maternal breast milk. It has been shown that breast milk intake is advantageous for physical and mental development of neonates and should be the nutrition of choice.[47] If breast milk is unavailable, various specially formulated products can be used for bottle-feeding. Specialist nutrition support is required if neonates are too premature or weak to suck or swallow. These conditions are common in neonates below 32-34 weeks of gestation. In these cases, a nasogastric or transpyloric tube can be inserted to provide either breast milk or formula milk. If enteral feeding is not possible or insufficient to meet energy and nutrient requirement, parenteral nutrition is indicated.[131]

Adequate nutrition for neonates and specifically premature neonates is crucial for their growth and development.[132] In some cases, nutritional intake must be increased above normal requirement to promote catch-up growth if *in-utero* development was impaired.[133] Nutritional requirements have been estimated using various approaches including: extrapolation from healthy neonates and from in-uterus nutrient accretion,[22] and estimation of requirements by measuring energy expenditure.[134,135] Studies have been undertaken which distinguish between requirements for premature and surgical infants.[136-138] Current recommendations for macronutrient and energy intake for neonates are summarised in Table 4.1.

	Premature infants	Surgical infants
Amino acids (g/kg/day)	3.5-3.85■	2.5-3□
Glucose (g/kg/day)	14.4-18.7■	<18□
Lipids (g/kg/day)	3■	3-4•
Total energy (kcal/kg/day)	100-120■	90-100•

Table 4.1: Recommended macronutrient/energy intake in neonates (■[1]; □[139]; • [138])

In recent years, studies comparing conventional treatment with more aggressive nutrition support have been undertaken.[31,140,141] The term 'aggressive nutrition' has been defined as "practice that ranks towards the upper end of the range of established practices, or as practice that goes beyond the established and into untested territory".[142] Wilson and colleagues randomised two groups of sick very low birth weight infants. One group received nutritional support according to internal protocols, while the other received nutritional support according to a more aggressive protocol.[31] This more aggressive protocol included an earlier start of enteral feeds, administration of insulin in hyperglycaemia, administration of amino acids at amounts of up to 3 g/kg/day, and administration of more glucose and lipids. They found that total energy intake was significantly increased in the intervention group, but clinical outcome did not differ. Although growth did improve in the intervention group, it remained a problem in both groups. Porcelli and colleagues focused on the administration of amino acids for infants below 1000 g birth weight.[141] They compared nutritional intake and clinical outcomes in infants who received 3 g/kg/day with infants who received 4 g/kg/day amino acids. The study was designed as a temporal cohort study after a change in nutrition policy on their neonatal ward. Increased amino acid intake was largely from parenteral nutrition, and the increased intake was not found to cause metabolic disturbances. Thureen and colleagues investigated the safety of increased amino acid intake in the same patient group and found that intake of up to 3 g/kg/day was safe.[140] It is important to note in Porcelli's study that low amino acid intake was equivalent to the 'aggressive' intervention in the studies by Wilson and Thureen. Consequently, comparison of these studies is difficult and must be undertaken with caution. Both reports, however, concluded that an increase in nutritional intake was safe and that there is considerable potential for improving long-term outcome by such changes in nutrition policy. Review of the literature has shown that nutritional guidelines are available for neonates, and recommendations have been made to guide prescribers in choosing the appropriate amount and type of special nutrition care. A more recent focus has been the topic of

aggressive nutrition support, during which nutrition is increased more quickly than during more traditional regimens. A clear lack of information in the literature was identified regarding current prescribing practice and differences between prescribed and administered PN in neonatal patients.

It is therefore not known how recommendations made by international organisations are translated into practice. Additionally, the level of diversity within prescribing practice and the degree to which clinical factors might influence prescribing decisions is not known.

Understanding current practice is advantages as it informs prescribers about how their own practice compares to others in their field. It also enables assessment of quality of nutrition support.

Investigation of clinical practice can also highlight areas for improvement, especially with regard to the implementation of guidelines into practice.

4.1.2. Aims and objectives

The aim of this study was to characterise current UK and continental European nutrition support for neonates receiving PN, and thereby to evaluate the quality of neonatal specialist nutrition support. This was done in the form of external auditing.

In order to achieve this, the following parameters were measured: prescribed PN, differences between prescribed and administered PN, and total nutritional intake. The aim was also to assess diversity of prescribing practice within different types of hospitals in the UK in comparison to European centres.

This study was also designed to expand on previously explored use of standard solutions (StSol), as discussed in Chapter 3. The frequency of StSol use was recorded, and composition of prescribed PN was compared with StSol described in the literature, StSol used in previously surveyed hospitals, and StSol suggested by surveyed hospitals. This comparison allowed an analysis of feasibility of StSol in the light of current practice.

Beecroft and colleagues investigated StSol for neonates in a similar way, by analysing the number of times prescribers deviated from recommendations made by prescribing software.[143] They concluded that up to two-thirds of feeds could be administered as StSol. The conception of this study was partly related to the work undertaken by Beecroft and colleagues.

The focus of this study was neonates receiving PN, even though enteral nutrition intake was also investigated. It is important to note that results from this study are not representative for the entire neonatal special care population, but only for neonates receiving most of their nutrition from PN.

This study was conducted in neonates only, as it was estimated that, in order to have sufficient numbers of patients for group comparison, a relatively homogenous group of patients was required. Paediatric patients are very diverse in terms of age and indications for PN, so large numbers of patients would have to have been recruited to compare PN prescribing practice. It was decided that data collection in all paediatric age groups was not feasible and that the focus should be on neonates only.

4.2. Methods

4.2.1. Study centres (UK)

For this study, 145 hospitals in England, Wales, Scotland, and Northern Ireland were invited to participate, which represented all hospitals treating a minimum of 300 neonates per year listed in the 'Neonatal Nurses Association Yearbook 2001'. This was the only identifiable and reliable source of information about all neonatal care units in the UK. The booklet was also very useful for this purpose as it contained detailed information about the names and contacts number of the staff in each of the neonatal wards. This meant it was possible to send the invitations to a specific person in each hospital.

The cut-off point of 300 neonates per year was chosen, because it was predicted that a sufficient amount of PN would be prescribed in these hospitals to make data collection feasible.

Two options had been identified in order to collect data from a random sample of 5-8 hospitals in the UK. Firstly, 5-8 contacts could have been randomly chosen from all the contacts. They could have then been invited to participate. The decision was made that this process would be too lengthy, as many of the contacted hospitals were likely not to participate. The second option was to send the invitation to all contacts, and to then randomly choose participants from the interested contacts. This second option was chosen.

Invitations were sent to the medical director, ward manager or paediatric consultants on neonatal intensive or special care wards as available from the Yearbook (Appendix 4). Forty-nine hospitals initially replied to the invitation. They were sent a confidentiality agreement (for the purpose of protecting the intellectual property of the study design, data collection form, and proposal for statistical analysis) in order to view detailed study documentation (Appendix 5). Of the forty-nine initial respondents, twenty returned the confidentiality agreement. Ten hospitals agreed to participate within the given deadline, eight in England and two in Scotland. Although this original plan had been to include 5-8 hospitals, this number was increased to 10, due to the unexpected large interest.

Due to the delay in the responses, it was not possible to actually randomise participants, as suggested above. Hospitals were included as soon as they agreed to participate. This meant that it was not a true random selection.

Of the participating hospitals, six were teaching hospitals (TH) and four were general district hospitals (GH). The study protocol and plan of data analysis are presented in Appendix 6.

4.2.2. Study centres (Belgium, Germany, Finland, France, Sweden, UK)

International teaching hospitals (ITH) were recruited as the comparison group. The hospitals where the members of the European discussion group practised (as described in section 3.1.1 of this thesis) were invited to take part in the study. Six agreed to participate. One of the members of the discussion group was from a UK hospital, consequently one of the ITH was in the UK.

This comparison group was recruited, as it was deemed important to maintain an international scope to the project, but it was not feasible to conduct data collection by the same monitor in other European countries. Data from this group were analysed separately, and differences in data collection were considered in the discussion of the results as appropriate.

4.2.3. Data collection

Retrospective data collection took place in the UK between May and July 2002 by the author. It was not feasible to collect data prospectively, due to time constraints on the data collector, as the author of this thesis personally collected all data. Prospective data collection would have meant that the data collected had to spend 20 weeks in 10 different hospitals. In some cases more than two weeks per hospital would have been required, due to the small amount of PN used. Retrospective data collection meant that all data were collected in each hospital in 2-3 days, *i.e.* 25 days in total. The drawback of retrospective data collection was that all information collected had to be available from medical records or pharmacy compounding records.

In ITH centres, local monitors (as appointed by the members of the European discussion group) collected data prospectively over a two-week period during June and July 2002. Prospective data collection was feasible in ITH, as data collectors were based at the hospitals.

Hospitals were characterised by number of neonatal beds, number of neonatal intensive care beds, number of surgical neonates per year, and number of neonates treated per year with a birth weight below 1500 g. Information was collected about neonates' gender, birth weight, gestation, Apgar scores at one and five minutes, and about the

following medical problems or interventions: sepsis, surgery, metabolic disorder, congenital malformation of the gastrointestinal tract, fluid restriction, and organ failure. Discussions with members of the European discussion group had identified that these conditions would be the most relevant. These data were extracted from medical records. Information about prescribed PN was either available from the compounding pharmacy department or from medical records, and prescribed volume of binary solution (amino acids and glucose solution) (mL), lipid emulsion (mL), amino acids (g), glucose (g), sodium (mmol), and potassium (mmol) per day were recorded. Amounts of administered PN were extracted from fluid charts. The type of intravenous line used to administer PN was available either from medical records or fluid charts. Details were also recorded about the type and amounts of enteral feeding administered concurrently with PN, and amounts of additional non-nutritional fluids (*e.g.* medication, flushes, or clear fluids) given, excluding blood products. It was estimated that the collection of the exact type of additional non-nutritional fluids, especially regarding glucose, sodium, and potassium content, would be too complex and inaccurate, and would mostly be negligible compared to the amounts derived from nutrition. It was therefore decided that only the amount, not the exact composition, of additional fluids would be recorded. Data collection forms are attached in Appendix 7.

4.2.4. Electronic data capture tool

Investigators in ITH centres were given the option to use the same data collection forms as used in the UK or to electronically collect and transfer data. Because six different countries were involved, electronic storage and submission of data saved time and resources, provided data collectors with an easy to use interface, and potentially increased accuracy of data transfer into the final database, by reducing transcription errors. A Microsoft Access data capture tool was developed, details about which are available from the CD and examples in Appendix 8.

4.2.5. Patient population

Neonates less than twenty-eight days of age were included, independent of gestation, birth weight, or indication for PN. In the UK, data were collected retrospectively from neonates who had received PN in the two weeks prior to data collection, but in some hospitals this period had to be extended to up to five weeks due to the small number of neonates treated. In ITH centres, data were collected prospectively over a two-week

period. At least five neonates were included per hospital, and a minimum of fifteen nutrition days amongst all patients was collected per hospital. The maximum number of PN days per neonate was fourteen, in order to prevent data from being biased towards a small number of patients. Although this meant that long-term PN in neonates was not studied, the majority of patients were expected to have relatively short term PN (*e.g.* 5-10 days). It was envisaged that if data collection was allowed to take place for 28 days for any patient, the overall number of PN days would have been weighted towards a small number of patients (*e.g* 10 neonates could have accounted for 280 nutrition days). Data collection stopped if greater than half of nutrition volume was provided enterally or if the neonate reached the age of twenty-eight days.

4.2.6. Ethical considerations

The protocol and data collection forms for the UK part of the study were submitted as a research project to the South West Multicentre Ethics Committee for ethical consideration. The committee decided that this was an audit and would not require formal approval, as it was non-interventional and anonymous. The terminology of the documentation was therefore changed to 'Audit' (Appendix 3). It is important to point out that, although this project has characteristics of an audit, it cannot be classified as a traditional medical audit, especially as data were collected externally. To clarify this, the term audit was subsequently changed to 'study'.

It was pointed out that individual centres should receive feedback regarding their performance. This recommendation was followed, and a summary of results was sent to each hospital in confidence in October 2002. The letter from the Ethics committee is attached in the appendix. As the data collector was not an NHS employee, and access was required to patients' notes and fluid charts, honorary contract were singed with 8 of the 10 hospitals, the other two hospitals only required an agreements of confidentiality. International centres dealt with their local ethical committees as required. No special confidentiality considerations were necessary in international centres, as data collectors were employees of the hospital.

4.2.7. Data analysis

Data were analysed using the software SPSS 10.0 for Windows. Populations were compared by non-parametric Kruskal-Wallis H procedure. A maximum *P* value of 0.05 was chosen to represent statistical significance. Figures show means unless otherwise

stated, and error bars represent 95% confidence intervals. A one-way analysis of variance was applied to detect any interaction between 'Day of PN' and 'Body weight'. Unless otherwise stated, data were analysed separately for the three types of hospitals: GH, TH, and ITH. Data were shown as mean and standard deviation, if they were normally distributed. If data were skewed, median and interquartile ranges were shown.

Concentrations of prescribed macronutrients were compared to an empirically derived standard formula. The suggestion for this formula for comparison had been the result of the analysis of clinical and pharmaceutical requirements by the discussion group (as highlighted in Chapter 3). The standard solutions suggested contained 2.5 % amino acids, 12 % glucose, and 2 % lipids. The numbers of days were calculated when these standard concentrations would have fit the prescription (this method is closely related to the work by Beecroft and colleagues).[143]

4.2.8. Estimation of energy intake

Data collected allowed an estimation of energy intake. Due to the way in which data were collected (*e.g.* mL of nutrition volume), some assumption of caloric contents had to be made. It was assumed that breast milk contained on average 67 kcal/100 mL (1.2 g amino acids, 7.0 g glucose, 3.8 g lipids)[3]. Enteral formulae were calculated according to manufacturers' information as shown in Table 4.2.

In 100 mL	Nutriprem	Enfalac Premature	Pepti-Junior	SMA Gold
Amino acids (g)	2.4	2.3	2.0	1.5
Glucose (g)	7.9	8.3	7.2	7.2
Lipids (g)	4.4	3.8	3.7	3.6
Energy (kcal)	80	75	66.4	67

Table 4.2: Macronutrient and energy content of commercial enteral formulae

The caloric content of macronutrients was defined as 4 kcal/g for amino acids, 4 kcal/g for glucose, and 9 kcal/g for lipids.[Hackl, 1994 #378] Additional glucose administered with non-nutritional fluids was not recorded, as previously highlighted, this was considered insignificant. Consequently, the macronutrient and energy intake shown only relates to parenteral and enteral nutrition intake.

Information was only recorded regarding quantities of nutrition. Proprietary brands of amino acid solutions or lipid emulsions were not recorded.

4.3. Results

4.3.1. Demographics of participating hospitals

Hospitals were characterised by number of neonatal beds and the number of surgical and low-birth-weight neonates they typically treat in one year. Table 4.3 summarises hospital characteristics in the three types of hospitals.

Hospitals	GH (N=4)		TH (N=6)		ITH (N=6)	
	Mean	SD	Mean	SD	Mean	SD
Neonatal beds	20.0	5.2	34.8	7.7	22.2	14.4
Intensive care beds	5.3	3.3	10.0	2.5	14.4	9.2
Surgical neonates per year	1.0	2.0	57.0	97.5	61.3	22.5
Neonates <1500 g birth weight per year	49.0	19.3	118.6	23.9	98.5	50.2

Table 4.3: Demographics of participating hospitals

4.3.2. Patient demographics

A total of 142 neonates were included in this study, 30 in GH, 60 in TH, and 52 in ITH. They were segmented by birth-weight, gestation, and Apgar scores at one and five minutes. The age at which PN was first prescribed was also recorded. Among all neonates, mean birth weight was 1459 ± 814 g and mean gestational age was 30.3 ± 4.3 weeks; 81 neonates (57%) were male and 61 (43%) were female. Most of the neonates (94%) were born prematurely (before 38 weeks of gestation). Additional or underlying problems were usually sepsis (GH 3 patients, TH 19 patients, ITH 9 patients) and surgery (GH 1 patient, TH 12 patients, ITH 13 patients). Also present were congenital malformations of the gastrointestinal tract (TH 1 patient, ITH 9 patients) and metabolic disorders (GH 1 patient, ITH 2 patients). In ITH, 2 patients were fluid restricted and 2 had organ failure. No additional or underlying problems other than prematurity were noted in 25 patients in GH (83%), 34 patients in TH (57%), and 26 patients in ITH (50%). Table 4.4 summarises data for each of the three types of hospitals.

	GH (N=30)	TH (N=60)	ITH (N=52)
	Mean ± SD	Mean ± SD	Mean ± SD
Birth weight (g)	1375 ± 699	1309 ± 696	1682 ± 954
Gestation (weeks)	30.0 ± 3.6	29.5 ± 3.9	31.5 ± 4.8
Gestation surgical neonates (weeks)	N/A	32.4 ± 4.1	32.4 ± 6.2
Gestation non-surgical neonates (weeks)	N/A	28.8 ± 3.6	31.2 ± 4.3
Apgar 1 min	6.6 ± 2.3	6.6 ± 2.2	6.2 ± 2.5
Apgar 5 min	8.5 ± 1.1	8.4 ± 1.9	7.8 ± 1.8
Age at first PN (days)	3.4 ± 1.8	2.5 ± 1.4	2.9 ± 4.6

Table 4.4: Patient demographics (N/A: not applicable)

There were apparent differences between the birth weight and gestation of neonates in GH, TH and ITH, but these were not statistically significant (birth weight P=0.099; gestation P=0.083). Surgical neonates were born significantly later in gestation than non-surgical neonates in TH (P=0.007).

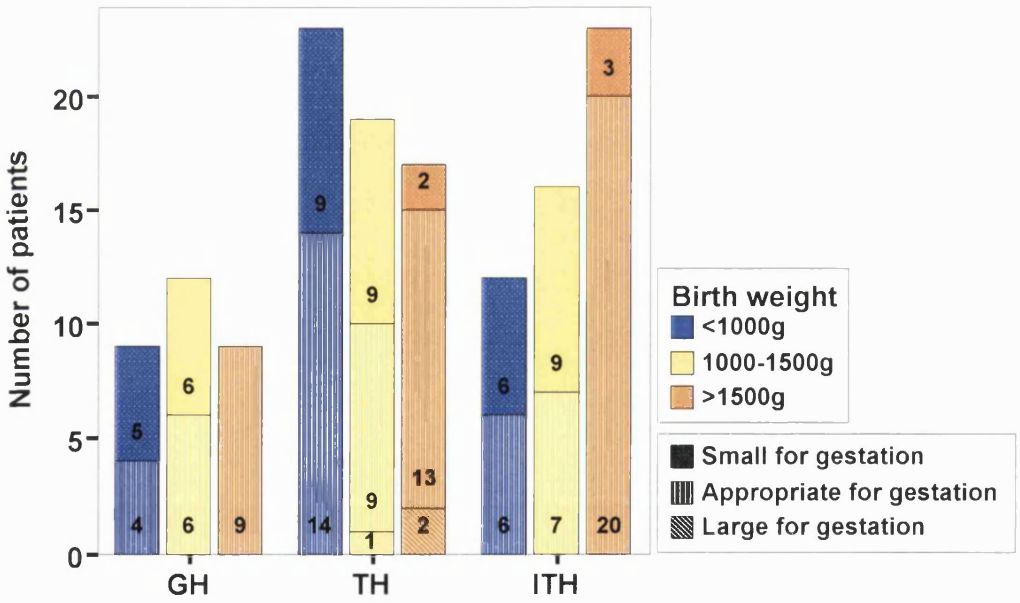

Figure 4.1: Appropriateness of weight for gestation in three birth weight groups

Birth weight and gestation data have been further analysed to identify neonates who are small, appropriate, and large for gestational age.

Small or large for gestational age was defined as values more than two standard deviations below or above the mean. Standard weight curves were used from Helsinki University Central Hospital, and the calculations were performed with the help of software at this hospital. Standard curve had been identified in the literature, but manual calculation was considered to be unnecessarily complex and time consuming.

The results showed that 62% percent of neonates were appropriate for gestation, 35% were small, and two percent were large for gestation. Appropriateness for gestation related to birth weight is shown in Figure 4.1.

Figure 4.2 shows the relationship between the age at the start of PN and the neonate's birth weight. PN was mostly started between the ages of two and three days, and there was no clear relationship between birth weight and start of PN.

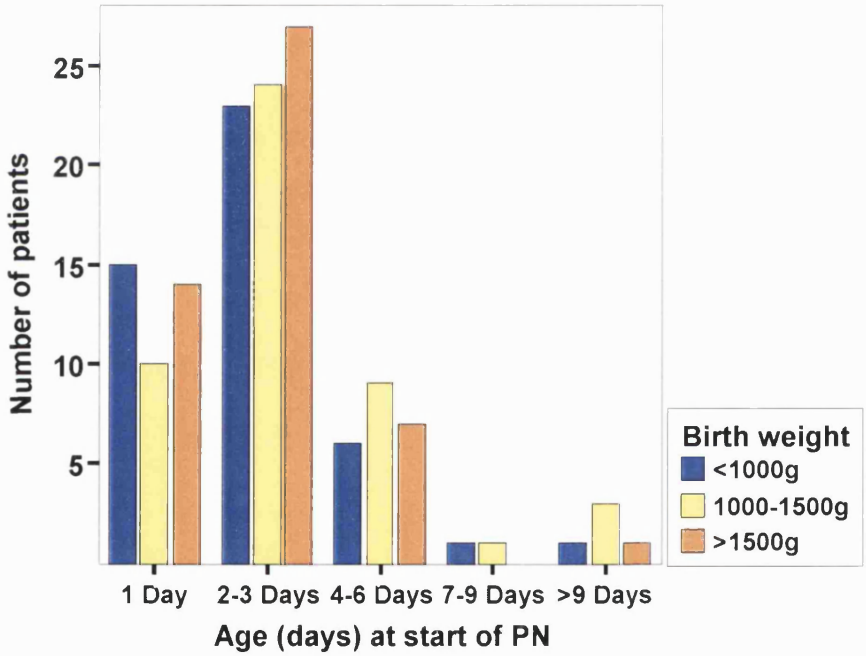

Figure 4.2: Age (days) when PN was first started in neonates depending on birth weight in all hospitals

4.3.3. Prescribed parenteral nutrition

One of the main objectives of the study was to investigate PN prescribing practice and a total of 752 nutrition days were collected (GH 118, TH 395, ITH 239). One patient in TH had been transferred between hospitals, and the starting date of PN was therefore not available. The five nutrition days related to this patient are therefore missing when the 'Day of PN' is shown.

Sub-population: Day of PN

Data were split into different days of PN (1st Day; 2nd-3rd Day; 4th-6th Day; 7th-9th Day; >9th Day) to take into account that PN was introduced slowly over several days. This was a slight deviation from the plan of analysis, but it was realised during data collection and preliminary data analysis that PN was sometimes advanced over more than a week. Table 4.5 summarises prescribed PN for GH, Table 4.6 for TH, and Table 4.7 for ITH. The values shown for lipids only relate to days when lipids were prescribed, *i.e.* zero values were treated as missing data.

GH	Day 1	Days 2-3	Days 4-6	Days 7-9	Days >9
(per kg/day)	N=26	N=45	N=29	N=8	N=10
Binary solution (mL)	84.8 ± 33.6	103.9 ± 34.8	116.6 ± 30.3	130.4 ± 44.3	116.1 ± 29.6
Amino acids (g)	0.9 ± 0.5	1.5 ± 0.5	2.0 ± 0.5	1.6 ± 0.5	1.8 ± 0.5
Glucose (g)	9.6 ± 3.4	12.0 ± 3.5	14.5 ± 2.2	14.2 ±4.3	14.1 ± 3.2
Sodium (mmol)	1.2 ±1.3	1.5 ± 1.5	2.4 ± 1.7	2.6 ± 1.7	4.2 ± 1.3
Potassium (mmol)	1.5 ± 1.0	1.7 ± 0.9	1.9 ± 0.6	1.9 ± 0.5	2.0 ± 0.6
	N=6	N=26	N=20	N=7	N=9
Lipids (g)	1.2 ± 0.6	1.3 ± 0.6	2.3 ± 0.8	1.5 ± 1.0	2.2 ± 0.9

Table 4.5: Prescribed PN in GH at different days of PN (mean ± SD)

In GH, volumes of binary solutions were increased to an average of 130 mL/kg/day over a week and showed large variability. Macronutrient prescriptions were also very variable, and they reached highest levels after four to six days of PN.

Prescribed amounts of binary solution were observed at lower levels in TH than in GH (128 mL/kg/day), but they were equally variable. Macronutrients increased over more than nine days of PN and amino acids were prescribed in much larger amounts.

Prescribed potassium was similar in both types of hospitals, whereas more sodium was prescribed in TH.

TH	Day 1	Days 2-3	Days 4-6	Days 7-9	Days >9
(per kg/day)	N=37	N=95	N=107	N=82	N=69
Binary solution (mL)	81.5 ± 28.1	100.5 ± 32.5	110.3 ± 35.5	108.4 ± 33.7	107.3 ± 33.7
Amino acids (g)	1.3 ± 0.8	1.9 ± 0.8	2.3 ± 0.8	2.5 ± 0.8	2.8 ± 0.9
Glucose (g)	9.4 ± 3.2	10.8 ± 3.1	13.1 ± 2.9	13.6 ± 3.2	13.8 ± 3.0
Sodium (mmol)	2.5 ± 1.2	2.5 ± 1.1	3.2 ± 1.5	3.6 ± 1.7	3.6 ± 1.4
Potassium (mmol)	1.6 ± 0.8	1.7 ± 0.7	2.1 ± 0.7	2.1 ± 0.6	2.0 ± 0.6
	N=20	N=76	N=103	N=82	N=69
Lipids (g)	0.9 ± 0.4	1.4 ± 0.8	2.0 ± 1.0	2.5 ± 1.2	2.6 ± 0.9

Table 4.6: Prescribed PN in TH at different days of PN (mean ± SD)

Macronutrients were increased similarly to TH, but less sodium and potassium were prescribed.

ITH	Day 1	Days 2-3	Days 4-6	Days 7-9	Days >9
(per kg/day)	N=33	N=66	N=66	N=38	N=36
Binary solution (mL)	58.2 ± 34.0	70.9 ± 33.9	94.6 ± 38.2	113.8 ± 45.5	113.5 ± 34.3
Amino acids (g)	0.9 ± 0.6	1.5 ± 0.6	2.1 ± 0.6	2.6 ± 0.6	2.7 ± 0.4
Glucose (g)	7.3 ± 2.8	9.1 ± 3.4	12.1 ± 4.0	14.6 ± 4.1	14.7 ± 5.3
Sodium (mmol)	1.2 ± 1.6	1.6 ± 1.5	2.3 ± 1.2	2.6 ± 1.1	1.8 ± 1.7
Potassium (mmol)	0.7 ± 0.7	1.1 ± 0.7	1.8 ± 0.9	2.1 ± 0.5	2.0 ± 1.0
	N=8	N=28	N=35	N=30	N=30
Lipids (g)	0.7 ± 0.4	1.1 ± 0.7	1.8 ± 1.0	1.9 ± 1.0	2.3 ± 0.7

Table 4.7: Prescribed PN in ITH at different days of PN (mean ± SD)

Differences in prescribed PN were significant between the three types of hospitals on the following days (Table 4.8):

Day of PN		Binary volume (mL/kg)	Amino acids (g/kg)	Glucose (g/kg)	Lipids (g/kg)	Sodium (mmol/kg)	Potassium (mmol/kg)
1	χ^2	14.0	13.3	8.7	3.8	20.2	20.1
	P	0.001	0.001	0.013	0.143	0.000	0.000
2-3	χ^2	35.9	11.7	20.1	1.4	28.6	23.7
	P	0.000	0.003	0.000	0.474	0.000	0.000
4-6	χ^2	11.6	6.3	12.3	5.9	26.9	10.2
	P	0.003	0.042	0.002	0.050	0.000	0.006
7-9	χ^2	2.0	12.7	1.4	9.9	13.3	0.4
	P	0.361	0.002	0.484	0.007	0.001	0.791
>9	χ^2	.9	12.0	0.0	9.6	34.6	0.1
	P	0.611	0.002	0.969	0.008	0.000	0.960

Table 4.8: Analysis of statistical significance in PN prescribing practice between the three types of hospitals

Sub-population: Body weight

Amino acids and glucose prescriptions were analysed separately for three body weight groups: <1000 g; 1000 – 1500 g; >1500 g. These body weight groupings were designed in order to help identify if weight played a significant role in prescribing decisions. Data are shown in Table 4.9 for GH, in Table 4.10 for TH, and in Table 4.11 for ITH.

Body weight		< 1000 g		1000 – 1500 g		> 1500 g		χ^2	*P*
GH		N	Mean ± SD	N	Mean ± SD	N	Mean ± SD		
Amino acids (g/kg/day)	Day 1	9	1.0 ± 0.6	11	1.0 ± 0.5	6	0.5 ± 0.2	3.5	0.175
	Days 2-3	18	1.4 ± 0.5	15	1.6 ± 0.5	12	1.6 ± 0.6	1.8	0.412
	Days 4-6	15	1.8 ± 0.4	5	2.2 ± 0.2	9	2.3 ± 0.5	10.1	0.006
	Days 7-9	6	1.7 ± 0.0	2	1.3 ± 1.1	0	-	0.0	1.000
	Days >9	5	1.7 ± 0.0	5	2.0 ± 0.7	0	-	0.3	0.577
Glucose (g/kg/day)	Day 1	9	9.9 ± 3.2	11	9.5 ± 3.9	6	9.5 ± 3.5	0.0	0.988
	Days 2-3	18	13.0 ± 3.1	15	10.9 ± 3.6	12	11.6 ± 3.6	2.2	0.333
	Days 4-6	15	14.4 ± 2.7	5	14.2 ± 0.8	9	14.7 ± 2.2	0.3	0.893
	Days 7-9	6	15.0 ± 4.7	2	11.8 ± 2.5	0	-	0.4	0.505
	Days >9	5	16.3 ± 1.0	5	11.9 ± 3.1	0	-	6.8	0.009

Table 4.9: Glucose and amino acids prescribed for infants of different body weight in GH

Amino acid prescriptions in GH did not show differences for neonates of different weight. Although it reached statistical significance on days four to six, there was no general pattern of amino acid prescriptions for smaller or larger neonates. In TH, the tendency was to prescribe more amino acids for smaller neonates, but this only reached significance after nine days. The trend was, however, to prescribe more glucose, and this was significant on days four to nine. In ITH, less amino acid and more glucose were prescribed for smaller neonates.

The overall picture was that prescription did not differ greatly for smaller or larger infants. There was a slight tendency for smaller infants to be prescribed more amino acids and less glucose in TH and ITH.

Body weight		< 1000 g		1000 – 1500 g		> 1500 g		χ^2	P
TH		N	Mean ± SD	N	Mean ± SD	N	Mean ± SD		
Amino acids (g/kg/day)	Day 1	13	1.6 ± 0.9	11	1.3 ± 0.9	13	1.1 ± 0.3	1.8	0.407
	Days 2-3	40	2.1 ± 0.9	31	1.9 ± 0.9	24	1.7 ± 0.6	3.9	0.140
	Days 4-6	54	2.4 ± 0.9	33	2.3 ± 0.8	20	2.2 ± 0.6	0.2	0.883
	Days 7-9	48	2.6 ± 0.9	21	2.4 ± 0.9	13	2.3 ± 0.4	0.8	0.666
	Days >9	39	2.8 ± 1.1	23	2.9 ± 0.6	7	2.0 ± 0.3	6.2	0.046
Glucose (g/kg/day)	Day 1	13	9.1 ± 4.0	11	10.3 ± 3.3	13	9.1 ± 2.4	1.1	0.581
	Days 2-3	40	10.4 ± 3.3	31	11.5 ± 3.0	24	10.5 ± 2.7	2.6	0.271
	Days 4-6	54	12.8 ± 2.6	33	12.9 ± 2.2	20	14.2 ± 4.2	6.0	0.045
	Days 7-9	48	13.1 ± 2.8	21	13.4 ± 3.0	13	15.9 ± 4.3	12.1	0.002
	Days >9	39	13.8 ± 3.0	23	14.5 ± 2.2	7	11.8 ± 4.6	3.1	0.218

Table 4.10: Glucose and amino acids prescribed for infants of different body weight in TH

Body weight		< 1000 g		1000 – 1500 g		> 1500 g		χ^2	*P*
ITH		N	Mean ± SD	N	Mean ± SD	N	Mean ± SD		
Amino acids (g/kg/day)	Day 1	9	0.9 ± 0.5	9	0.9 ± 0.7	15	0.9 ± 0.5	0.0	0.982
	Days 2-3	21	1.8 ± 0.8	16	1.7 ± 0.6	29	1.3 ± 0.4	8.1	0.017
	Days 4-6	17	2.6 ± 0.7	20	2.0 ± 0.5	29	1.9 ± 0.5	11.8	0.003
	Days 7-9	15	2.8 ± 0.6	9	2.2 ± 0.5	14	2.5 ± 0.4	5.9	0.052
	Days >9	8	2.7 ± 0.4	18	2.7 ± 0.5	10	2.7 ± 0.5	0.7	0.691
Glucose (g/kg/day)	Day 1	9	7.2 ± 2.7	9	8.2 ± 3.5	15	6.9 ± 2.4	0.9	0.641
	Days 2-3	21	9.1 ± 3.3	16	11.0 ± 3.8	29	8.2 ± 2.8	7.5	0.024
	Days 4-6	17	11.5 ± 4.0	20	12.5 ± 4.5	29	12.1 ± 3.7	0.6	0.728
	Days 7-9	15	14.3 ± 3.8	9	13.1 ± 5.5	14	15.9 ± 3.5	2.1	0.355
	Days >9	8	12.0 ± 3.9	18	12.9 ± 4.6	10	19.9 ± 3.9	12.0	0.002

Table 4.11: Glucose and amino acids prescribed for infants of different body weight in ITH

Sub-population: Type of PN

PN was either given as sole means of feeding or concurrently with EN. Data have been analysed separately for days when neonates received full PN and partial PN, in order to examine if concurrent enteral feeding affected PN prescribing. Full PN referred to days when at least 90 % of feeding volume was PN; partial PN refers to days when between 50% and 90% of feeding volume was PN. The plan of analysis had set out to refer to full PN if 80-100 % of nutrition volume was from PN. This had been based on the assumption that enteral feeding would be given on the majority of PN days. This was subsequently changed to 90-100 %, as EN was not administered on a large number of days, in order to achieve a more equal distribution in the two groups.

Table 4.12 shows prescribed amounts of macronutrients in GH. There was a tendency for higher amounts of amino acids in partial PN that was only significant after nine days of PN. The overall trend, however, was that concurrent enteral feeding did not influence PN prescriptions.

GH		Full PN		Partial PN		Kruskal-Wallis	
		N	Mean ± SD	N	Mean ± SD	$\chi 2$	*P*
Amino acids (g/kg/day)	Day 1	19	1.0 ± 0.6	7	0.6 ± 0.2	2.2	0.138
	Days 2-3	25	1.3 ± 0.5	20	1.7 ± 0.6	4.3	0.977
	Days 4-6	13	1.9 ± 0.4	16	2.1± 0.5	0.8	0.368
	Days 7-9	4	1.4 ± 0.6	4	1.8 ± 0.2	0.4	0.508
	Days >9	6	1.6 ± 0.3	4	2.3 ± 0.6	5.2	0.023
Glucose (g/kg/day)	Day 1	19	9.6 ± 3.5	7	9.7 ± 3.5	0.0	0.977
	Days 2-3	25	11.9 ± 3.7	20	12.0 ± 3.2	0.1	0.749
	Days 4-6	13	13.6 ± 5.7	16	12.8 ± 3.8	2.6	0.104
	Days 7-9	4	16.1 ± 4.3	4	9.2 ± 6.5	3.0	0.083
	Days >9	6	14.2 ± 4.2	4	13.9 ± 0.6	0.7	0.394
Lipids (g/kg/day)	Day 1	6	1.2 ± 0.6	0	-	-	-
	Days 2-3	14	1.4 ± 0.6	12	1.1 ± 0.6	1.8	0.181
	Days 4-6	7	1.8 ± 0.9	13	2.5 ± 0.6	2.8	0.096
	Days 7-9	3	0.7 ± 0.3	4	2.0 ± 1.0	3.9	0.050
	Days >9	6	1.9 ± 0.7	3	2.9 ± 0.8	2.0	0.154

Table 4.12: Prescribed amounts of macronutrients depending on type of PN in GH

Prescriptions in TH are summarised in Table 4.13. As reported for GH, there was no clear tendency for higher or lower prescribed amounts of macronutrients in full or partial PN.

TH		Full PN		Partial PN		Kruskal-Wallis	
		N	Mean ± SD	N	Mean ± SD	$\chi 2$	*P*
Amino acids (g/kg/day)	Day 1	31	1.3 ± 0.7	6	1.7 ± 1.1	1.1	0.303
	Days 2-3	64	2.1 ± 0.8	31	1.5 ± 0.8	14.6	0.000
	Days 4-6	65	2.3 ± 0.7	42	2.4 ± 1.0	0.6	0.450
	Days 7-9	53	2.5 ± 0.8	29	2.4 ± 0.9	0.7	0.396
	Days >9	40	2.9 ± 0.9	29	2.6 ± 0.9	2.3	0.127
Glucose (g/kg/day)	Day 1	31	8.7 ± 2.4	6	13.4 ± 4.4	5.7	0.017
	Days 2-3	64	11.2 ± 2.8	31	9.8 ± 3.4	6.4	0.011
	Days 4-6	65	13.3 ± 3.0	42	12.7 ± 2.8	0.5	0.485
	Days 7-9	53	13.6 ± 3.3	29	13.6 ± 3.3	0.0	0.911
	Days >9	40	14.1 ± 2.9	29	13.3 ± 3.1	0.6	0.426
Lipids (g/kg/day)	Day 1	18	0.9 ± 0.4	2	0.8 ± 0.4	0.0	0.900
	Days 2-3	56	1.5 ± 0.8	20	1.1 ± 0.7	3.3	0.068
	Days 4-6	64	1.9 ±1.0	39	2.2 ± 0.9	3.4	0.065
	Days 7-9	53	2.7 ± 1.1	29	2.0 ± 1.1	5.2	0.023
	Days >9	40	2.6 ± 0.9	29	2.6 ± 0.1	0.1	0.784

Table 4.13: Prescribed amounts of macronutrients depending on type of PN in TH

In ITH, however, significantly less amino acids and glucose were prescribed if neonates received substantial amounts of concurrent EN (Table 4.14), although these differences were not reflected in the prescribed lipid.

ITH		Full PN		Partial PN		Kruskal-Wallis	
		N	Mean ± SD	N	Mean ± SD	$\chi 2$	*P*
Amino acids (g/kg/day)	Day 1	23	1.0 ± 0.6	10	0.5 ± 0.2	5.0	0.026
	Days 2-3	36	1.8 ± 0.7	30	1.2 ± 0.4	12.2	0.000
	Days 4-6	35	2.3 ± 0.6	31	1.9 ± 0.5	7.2	0.007
	Days 7-9	23	2.8 ± 0.5	15	2.3 ± 0.6	9.7	0.002
	Days >9	27	2.7 ± 0.4	9	2.7 ±0.4	0.3	0.596
Glucose (g/kg/day)	Day 1	23	7.8 ± 3.0	10	6.2 ± 1.8	2.2	0.137
	Days 2-3	36	10.1 ± 3.6	30	8.1 ± 2.7	6.3	0.012
	Days 4-6	35	12.9 ± 3.2	31	11.2 ± 4.7	3.8	0.052
	Days 7-9	23	16.6 ± 3.5	15	11.4 ± 3.0	15.2	0.000
	Days >9	27	15.2 ± 5.3	9	13.0 ± 5.5	0.9	0.351
Lipids (g/kg/day)	Day 1	7	0.8 ± 0.3	1	0.2 ± 1.2	1.2	0.272
	Days 2-3	20	1.2 ± 1.2	8	0.9 ± 0.5	0.6	0.445
	Days 4-6	16	2.3 ± 2.3	19	1.1 ± 0.5	8.0	0.005
	Days 7-9	19	1.9 ± 1.9	11	2.0 ± 1.3	0.1	0.829
	Days >9	21	2.3 ± 2.3	9	2.2 ± 1.8	1.8	0.182

Table 4.14: Prescribed amounts of macronutrients depending on type of PN in ITH

Sub-population: Surgical neonates

Twenty percent of neonates in TH and twenty-five percent of neonates in ITH underwent surgery. Table 4.15 compares prescribed amounts of amino acids, glucose, and lipids in surgical and non-surgical neonates in both TH and ITH. There was a small tendency to prescribe more macronutrients to surgical patients, especially amino acids and lipids. GH are not included, as only one patient underwent surgery in this group.

TH and ITH		Surgical		Non-surgical		Kruskal-Wallis	
		N	Mean ± SD	N	Mean ± SD	$\chi 2$	p
Amino acids (g/kg/day)	Day 1	15	1.3 ± 0.6	55	1.1 ± 0.7	2.3	0.127
	Days 2-3	36	2.1 ± 0.7	125	1.7 ± 0.8	11.7	0.001
	Days 4-6	55	2.4 ± 0.5	118	2.2 ± 0.8	5.0	0.025
	Days 7-9	45	2.7 ± 0.6	75	2.4 ± 0.8	10.0	0.002
	Days >9	50	2.9 ± 0.7	55	2.6 ± 0.8	3.4	0.066
Glucose (g/kg/day)	Day 1	15	8.1 ± 0.7	55	8.6 ± 3.4	0.0	0.869
	Days 2-3	36	10.6 ± 2.4	125	10.0 ± 3.5	1.7	0.187
	Days 4-6	55	13.1 ± 3.5	118	12.5 ± 3.3	0.6	0.438
	Days 7-9	45	15.7 ± 3.5	75	12.9 ± 3.2	19.7	0.000
	Days >9	50	13.5 ± 3.9	55	14.6 ± 4.0	0.9	0.357
Lipids (g/kg/day)	Day 1	8	0.8 ± 0.3	20	0.9 ± 0.4	0.6	0.460
	Days 2-3	27	1.6 ± 0.7	77	1.2 ± 0.8	8.1	0.010
	Days 4-6	43	2.2 ± 1.0	95	1.7 ± 1.0	6.0	0.010
	Days 7-9	43	2.6 ± 0.9	69	2.2 ± 1.2	4.1	0.043
	Days >9	49	2.7 ± 0.7	50	2.4 ± 1.0	0.9	0.357

Table 4.15: Prescribed amounts of macronutrients to surgical and non-surgical neonates in TH and ITH

4.3.4. Interactions between 'Day of parenteral nutrition' and 'Body weight'

It has been established that prescriptions were significantly different depending on the day of PN and, in some instances, for neonates of different weight. By using one-way analysis of variance, this section will examine potential interactions between the two groups 'Day of PN' and 'Body weight' to establish if these reached levels of significance. Data are only shown for TH and ITH, because the amount of data available from GH is insufficient for this analysis.

The following figures show data for amino acids, glucose, lipid prescriptions, and the level of significance of difference between day of PN and body weight. The three separate lines represent different body weight groups. The horizontal axis represents different days of PN, and the vertical axis shows increasing amounts of prescribed macronutrient. The level of parallelism of the three lines defines the level of interaction, *i.e.* the more parallel they are the least do the factors interact.

Amino acid prescriptions in TH are shown in Figure 4.3. Larger neonates were prescribed less amino acid than smaller neonates after nine days of PN, but the interaction was not significant.

Figure 4.4 shows the same data for ITH. Again, there was no significant interaction, but smaller neonates tended to be prescribed more amino acids. The main difference between TH and ITH was that after nine days of PN larger neonates were prescribed less amino acid in TH, whereas, in ITH, they were prescribed the same amounts.

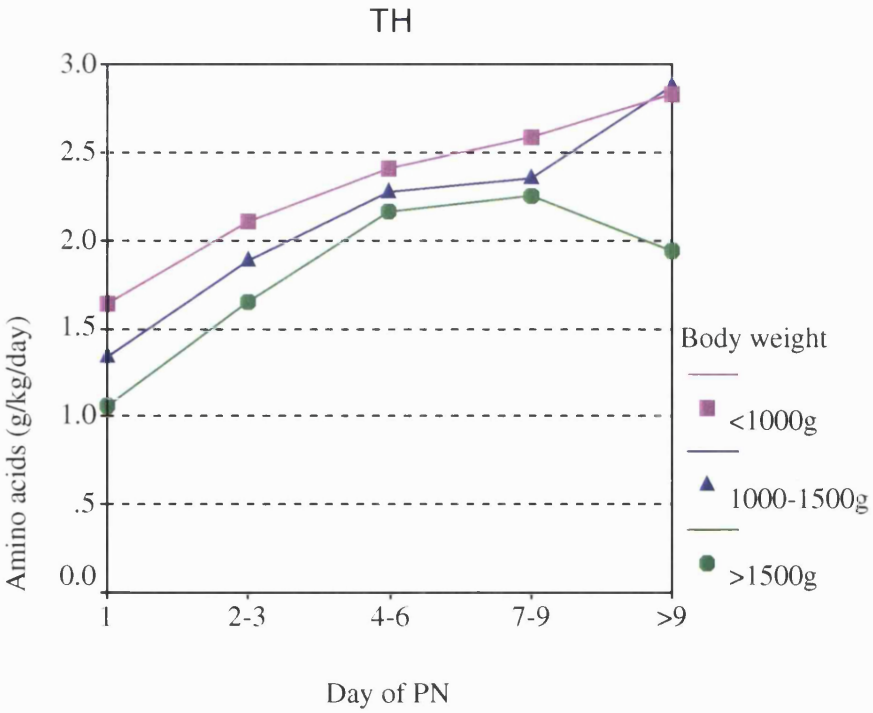

Figure 4.3: Prescribed amino acids (mean) in TH; significant differences for 'Day of PN' (*P*=0.000) and 'Body weight' (*P*=0.000); interaction not significant (*P*=0.748)

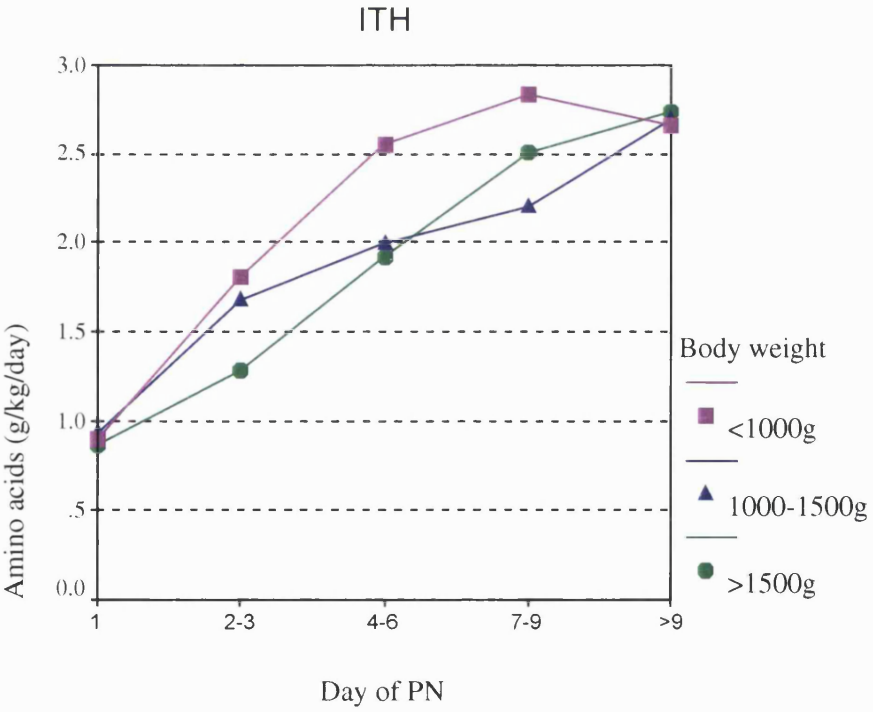

Figure 4.4: Prescribed amino acids (mean) in ITH; significant differences for 'Day of PN' (*P*=0.000) and 'Body weight' (*P*=0.005); interaction not significant (*P*=0.060)

The slopes for glucose prescriptions in TH are not parallel, and there is an interaction between day of PN and weight (Figure 4.5). Neonates over 1000 g were prescribed similar amounts, but smaller neonates were prescribed more glucose between the fourth and ninth day of PN and less after the ninth day.

There was also an interaction in ITH, but, unlike TH, neonates weighing over 1500 g received constantly increasing amounts of glucose, whereas glucose prescriptions for neonates below 1500g levelled out at 12-14 g/kg/day (Figure 4.6).

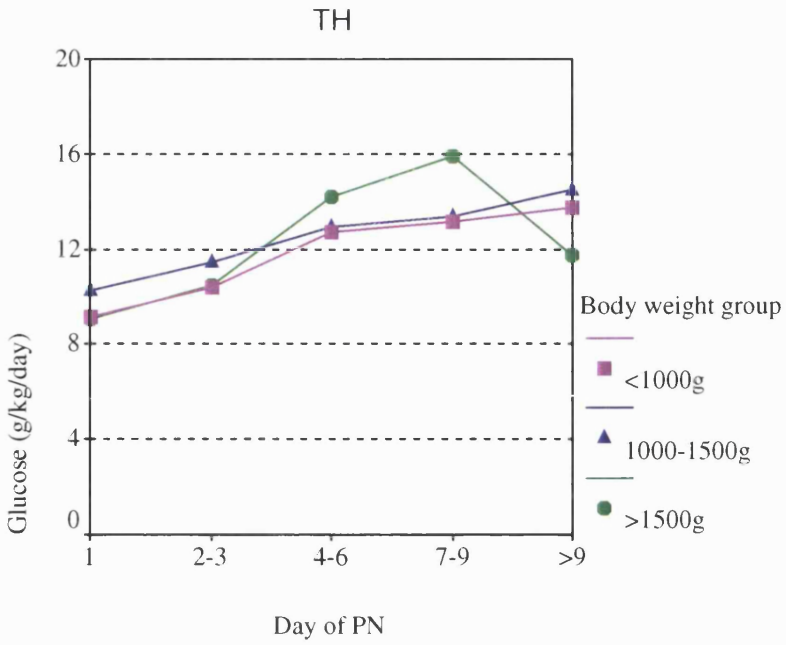

Figure 4.5: Prescribed glucose (mean) in TH; significant differences for 'Day of PN' (*P*=0.000) and 'Body weight' (*P*=0.206); significant interaction (*P*=0.050)

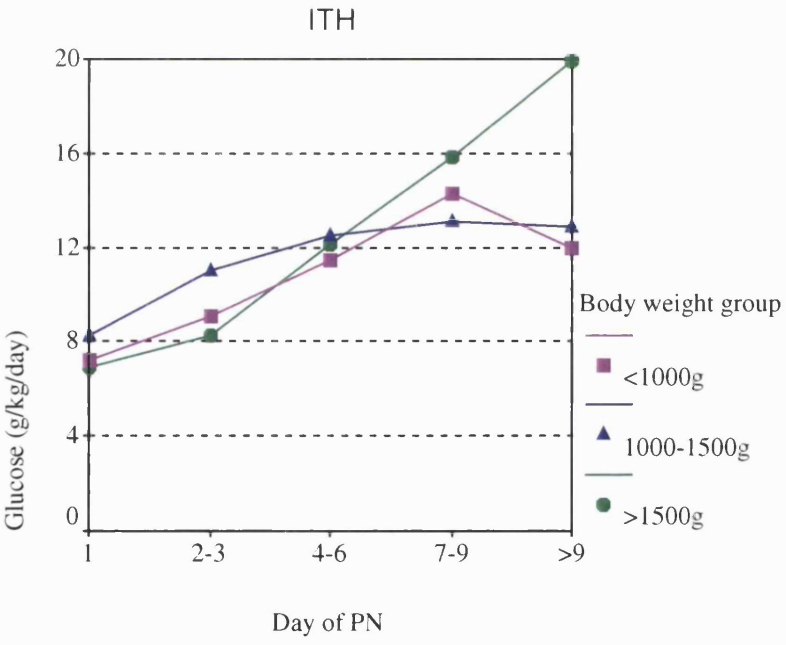

Figure 4.6: Prescribed glucose (mean) in ITH; significant differences for 'Day of PN' (*P*=0.000) and 'Body weight' (*P*=0.016); significant interaction (*P*=0.000)

Prescribed amounts of lipids were similar in both TH and ITH, and there was no significant interaction (Figure 4.7 and Figure 4.8).

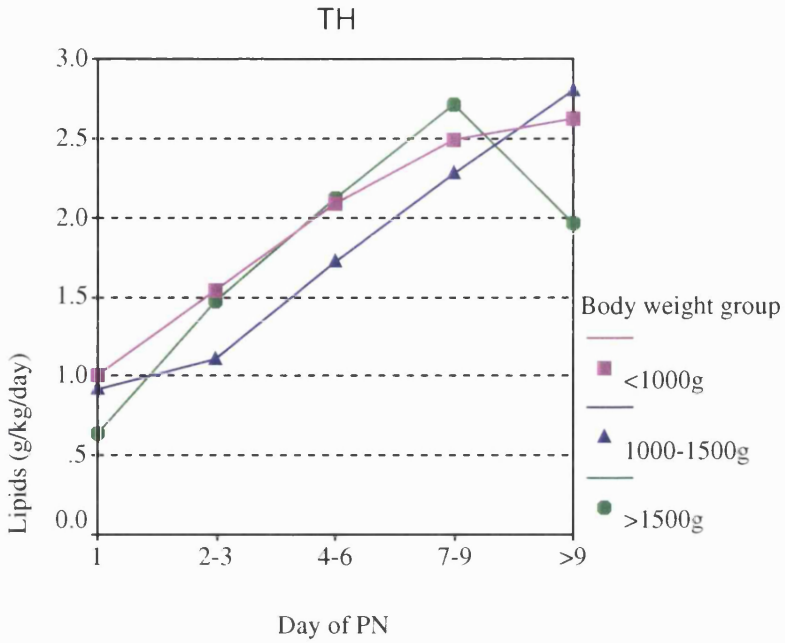

Figure 4.7: Prescribed lipids (mean) in TH; significant differences for 'Day of PN' (*P*=0.000) and 'Body weight' (*P*=0.333); interaction not significant (*P*=0.309)

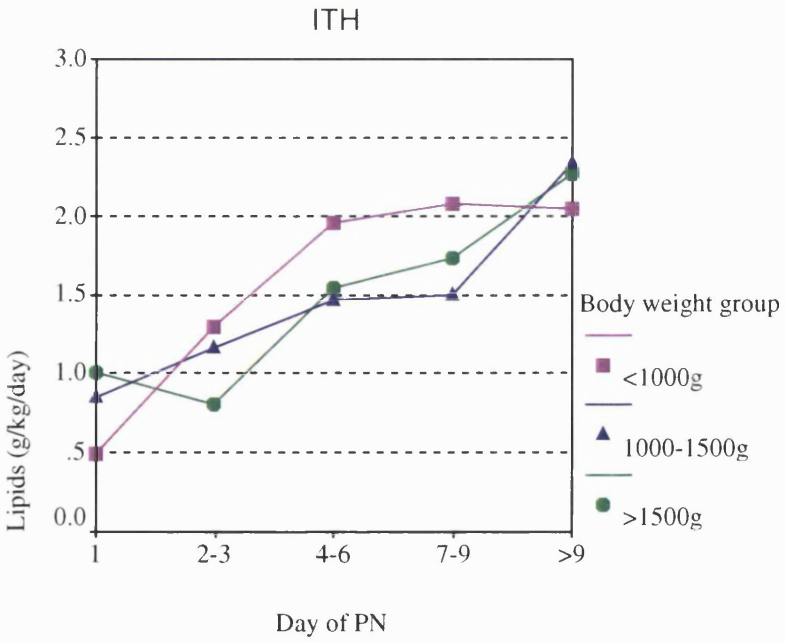

Figure 4.8: Prescribed lipids (mean) in ITH; significant differences for 'Day of PN' (*P*=0.000) and 'Body weight' (*P*=0.839); interaction not significant (*P*=0.799)

Lipids were increased steadily over nine days until reaching just over 2.5 g/kg/day in TH, and 2 g/kg/day in ITH. In TH, neonates weighing more than 1500 g were prescribed fewer lipids after nine days of PN, but this was not significant.

4.3.5. Concentrations of prescribed parenteral nutrition

Chapter 3 of this thesis focused on the use of StSol and potential concentrations of nutrients in PN. In order to analyse results of this study with regard to StSol, prescribed amounts of macronutrients were converted into concentrations. As lipids were usually given separately (in 98% of cases), only the binary solution has been used for these calculations.

Table 4.16 summarises concentrations of amino acids and glucose in prescribed amounts of binary solution in three different weight groups in GH. None of the weight groups showed a statistically significant difference, and mean values were very consistent throughout the increasing days of PN. Mean amino acid concentration were 1.2 % and mean glucose concentration 10 %.

Body weight		< 1000 g		1000 – 1500 g		> 1500 g		χ^2	P
GH		N	Mean ± SD	N	Mean ± SD	N	Mean ± SD		
Amino acids (g/100 mL)	1st Day	9	1.2 ± 0.8	11	1.2 ± 0.7	6	0.7 ± 0.7	2.8	0.252
	2nd-3rd Day	18	1.1 ±0.5	15	1.5 ± 0.5	12	1.4 ± 0.7	4.5	0.107
	4th-6th Day	15	1.3 ± 0.4	5	1.9 ± 0.6	9	1.6 ± 0.4	3.6	0.168
	7th-9th Day	6	1.2 ± 0.5	2	1.0 ± 0.8	0	-	0.1	0.733
	>9th Day	5	1.0 ± 0.1	5	1.4 ± 0.6	0	-	2.3	0.130
Glucose (g/100 mL)	1st Day	9	10.0 ± 0.7	11	9.9 ± 0.7	6	9.7 ± 0.8	0.8	0.672
	2nd-3rd Day	18	9.8 ± 0.7	15	10.1 ± 3.1	12	9.7 ± 2.1	0.3	0.852
	4th-6th Day	15	10.1 ± 0.6	5	12.4 ± 3.6	9	10.0 ± 1.0	3.0	0.222
	7th-9th Day	6	9.9 ± 2.7	2	8.4 ± 2.3	0	-	0.8	0.375
	>9th Day	5	10.0 ± 0.0	5	8.5 ± 2.3	0	-	2.8	0.095

Table 4.16: Concentration of amino acids and glucose in prescribed binary solution (GH)

The variability of concentrations was much larger in TH, especially for glucose (Table 4.17). Mean amino acid concentrations increased with increasing days of PN, but differences between weight groups were mainly non-significant. Glucose concentrations were different between weight groups with solutions for neonates below 1000 g containing 10 g/100 mL glucose and solutions for neonates above 1500 g containing 15g/100 mL glucose after nine days of PN. At earlier stages of PN, glucose concentrations were almost independent of body weight at around 10 g/100 mL.

Body weight		< 1000 g		1000 – 1500 g		> 1500 g		χ^2	P
TH		N	Mean ± SD	N	Mean ± SD	N	Mean ± SD		
Amino acids (g/100 mL)	1st Day	13	1.6 ± 0.7	11	1.3 ± 0.7	13	1.2 ± 0.5	2.4	0.301
	2nd-3rd Day	40	1.9 ± 0.5	31	1.6 ± 0.5	24	1.6 ± 0.5	9.7	0.008
	4th-6th Day	54	1.9 ± 0.5	33	1.8 ± 0.6	20	1.9 ± 0.7	0.4	0.811
	7th-9th Day	48	2.0 ± 0.6	21	1.9 ± 0.6	13	2.2 ± 0.7	1.4	0.490
	>9th Day	39	2.1 ± 0.5	32	2.3 ± 0.6	7	2.7 ± 1.1	2.9	0.231
Glucose (g/100 mL)	1st Day	13	9.3 ± 1.9	11	9.6 ± 0.9	13	9.9 ± 0.7	2.1	0.357
	2nd-3rd Day	40	9.4 ± 1.3	31	9.7 ± 1.2	24	10.2 ± 0.9	10.0	0.007
	4th-6th Day	54	10.0 ± 1.5	33	10.2 ± 1.6	20	11.9 ± 2.3	13.7	0.001
	7th-9th Day	48	10.1 ± 1.9	21	10.8 ± 1.5	13	14.1 ± 2.5	27.8	0.000
	>9th Day	39	10.3 ± 0.9	32	11.5 ± 2.6	7	15.0 ± 3.3	19.2	0.000

Table 4.17: Concentration of amino acids and glucose in prescribed binary solution (TH)

Concentrations of amino acids were very variable in ITH (Table 4.18). With the exception of the first day of PN, differences were significant between the weight groups. Reaching 3.1g/100 mL after nine days of PN, amino acid concentrations were highest for smaller neonates. Glucose concentrations also tended to be higher for smaller neonates, although this was less consistent.

Body weight		< 1000 g		1000 – 1500 g		> 1500 g		χ^2	*P*
ITH		N	Mean ± SD	N	Mean ± SD	N	Mean ± SD		
Amino acids (g/100 mL)	1st Day	9	1.3 ± 0.6	9	1.4 ± 0.5	15	1.4 ± 0.5	1.0	0.621
	2nd-3rd Day	21	2.5 ± 1.3	16	2.4 ± 2.2	29	1.8 ± 0.4	9.7	0.008
	4th-6th Day	17	3.2 ± 1.0	20	2.2 ± 0.7	29	1.8 ± 0.5	20.3	0.000
	7th-9th Day	15	2.7 ± 0.6	9	2.0 ± 0.6	14	2.0 ± 0.5	9.7	0.009
	>9th Day	8	3.1 ± 0.6	18	2.3 ± 0.3	10	2.0 ± 0.3	16.3	0.000
Glucose (g/100 mL)	1st Day	9	10.5 ± 4.7	9	13.5 ± 4.7	15	12.0 ± 3.3	2.3	0.319
	2nd-3rd Day	21	12.5 ± 6.1	16	15.1 ± 2.2	29	11.9 ± 2.9	7.8	0.021
	4th-6th Day	17	14.5 ± 5.8	20	13.2 ± 3.5	29	11.4 ± 2.9	5.7	0.030
	7th-9th Day	15	13.6 ± 3.6	9	11.1 ± 3.4	14	12.3 ± 1.7	3.7	0.160
	>9th Day	8	14.1 ± 5.3	18	10.5 ± 2.1	10	14.3 ± 1.2	11.4	0.003

Table 4.18: Concentration of amino acids and glucose in prescribed binary solution (ITH)

Concentrations of prescribed binary solution were further compared to an empirical standard, as described in the methods section. Prescriptions were considered to fit the proposed standard, if it was within 20% of the proposed concentration (*i.e.* 2-3g amino acids, 9.6-14.4g glucose, and 1.6-2.4 g lipids in 100 mL). Results were split into the different days of PN. Further analyses of 30% deviation from the suggested standard as described in the plan of analysis (Appendix 6) was not performed, because the 20% deviation exhibited a poor overall fit.

Most prescriptions on the first day of PN were below the empirical standard, but glucose showed a relatively good fit (Table 4.19).

1st Day		Below		Fit		Above	
		N	%	N	%	N	%
GH	Amino acids (g)	25	96	1	4	0	0
	Glucose (g)	6	23	20	77	0	0
	Lipids (g)	23	89	3	11	0	0
TH	Amino acids (g)	29	78	8	22	0	0
	Glucose (g)	20	54	17	46	0	0
	Lipids (g)	37	100	0	0	0	0
ITH	Amino acids (g)	30	91	3	9	0	0
	Glucose (g)	8	24	18	55	7	21
	Lipids (g)	33	100	0	0	0	0

Table 4.19: Number of first days of PN, where prescribed macronutrients fit the empirical standard

Prescriptions on the second and third days showed an overall better fit, especially in ITH (Table 4.20).

2nd-3rd Day		Below		Fit		Above	
		N	%	N	%	N	%
GH	Amino acids (g)	43	96	2	4	0	0
	Glucose (g)	22	49	22	49	1	2
	Lipids (g)	39	87	4	9	2	4
TH	Amino acids (g)	74	78	21	22	0	0
	Glucose (g)	57	60	38	40	0	0
	Lipids (g)	80	84	13	14	2	2
ITH	Amino acids (g)	36	55	24	36	6	9
	Glucose (g)	16	24	25	38	25	38
	Lipids (g)	56	85	8	12	2	3

Table 4.20: Number of days between 2nd and 3rd day of PN, where prescribed macronutrients fit the empirical standard

After the fourth day of PN, most prescriptions did not fit the standard (Table 4.21).

4^{th}-6^{th} Day		Below		Fit		Above	
		N	%	N	%	N	%
GH	Amino acids (g)	28	97	1	3	0	0
	Glucose (g)	15	52	13	45	1	3
	Lipids (g)	18	62	10	35	1	3
TH	Amino acids (g)	79	74	26	24	2	2
	Glucose (g)	61	57	46	43	0	0
	Lipids (g)	62	58	32	30	13	12
ITH	Amino acids (g)	32	49	24	36	10	15
	Glucose (g)	20	30	23	35	23	35
	Lipids (g)	50	76	10	15	6	9

Table 4.21: Number of days between 4^{th} and 6^{th} day of PN, where prescribed macronutrients fit the empirical standard

As more amino acids were prescribed in TH and ITH, more amino acid values fit the standard (Table 4.22). In GH, amino acid concentrations were always below the suggested standard, but glucose concentrations exhibited a better fit.

7^{th}-9^{th} Day		Below		Fit		Above	
		N	%	N	%	N	%
GH	Amino acids (g)	8	100	0	0	0	0
	Glucose (g)	3	38	5	63	0	0
	Lipids (g)	6	75	1	12	1	12
TH	Amino acids (g)	55	67	27	33	0	0
	Glucose (g)	42	51	39	48	1	1
	Lipids (g)	31	38	35	43	16	20
ITH	Amino acids (g)	18	47	18	47	2	5
	Glucose (g)	10	26	18	47	10	26
	Lipids (g)	23	61	8	21	7	18

Table 4.22: Number of days between 7^{th} and 9^{th} day of PN, where prescribed macronutrients fit the empirical standard

Finally, after nine days of PN, more prescriptions were within the standard range, but amino acid concentrations were mainly below suggested concentrations (Table 4.23).

>9th Day		Below		Fit		Above	
		N	%	N	%	N	%
GH	Amino acids (g)	9	90	1	10	0	0
	Glucose (g)	5	50	5	50	0	0
	Lipids (g)	7	70	2	20	1	10
TH	Amino acids (g)	30	43	37	54	2	3
	Glucose (g)	40	58	22	32	7	10
	Lipids (g)	21	30	30	44	18	26
ITH	Amino acids (g)	21	58	12	33	3	8
	Glucose (g)	11	31	18	50	7	19
	Lipids (g)	15	42	16	44	5	14

Table 4.23: Number of days after 9th day of PN, where prescribed macronutrients fit the empirical standard

4.3.6. Intravenous lipid emulsions

Intravenous lipids were administered on 68 days (58%) in GH, on 355 days (90%) in TH, and on 132 days (55%) in ITH. Lipid emulsions were usually infused separately from the binary solutions (97.3% of 555 days when lipids were given). All cases of lipid administration as TNA occurred in one particular ITH (fifteen cases). Number of days when lipids were administered to neonates are shown in detail in Figure 4.9 for GH, Figure 4.10 for TH, and Figure 4.11 for ITH. The left hand chart represents prescriptions for days when less than 10% of concurrent enteral feeding was given (Full PN); the right hand chart represents prescriptions for days when between 10 and 50% of concurrent enteral feeding was given (Partial PN). The scale of the y-axis was not standardised in each graph due to the large differences of data collected in each type of hospital.

Figure 4.9 shows that lipids were more likely to be started on the first day in GH, if full PN was given.

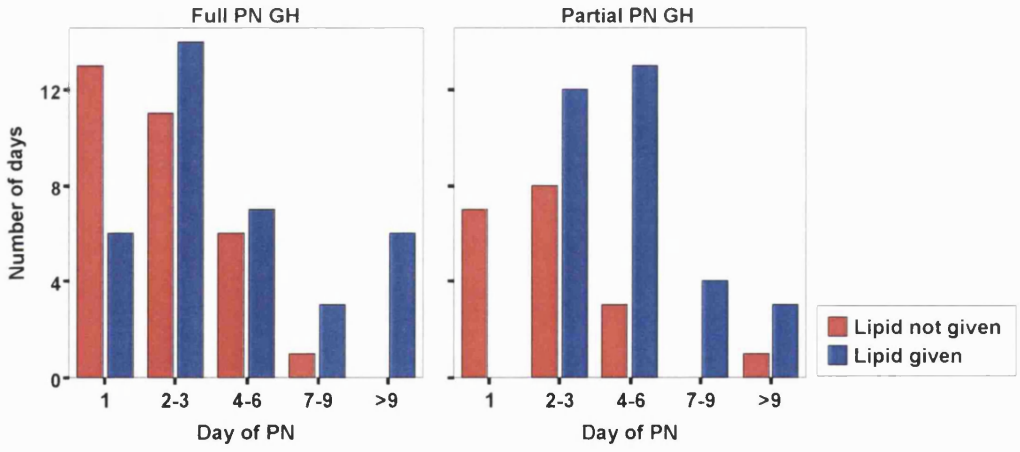

Figure 4.9: Number of days when lipids were administered in GH depending on concurrent enteral feeding

In TH, lipids were administered on most days of PN, regardless of enteral intake (Figure 4.10).

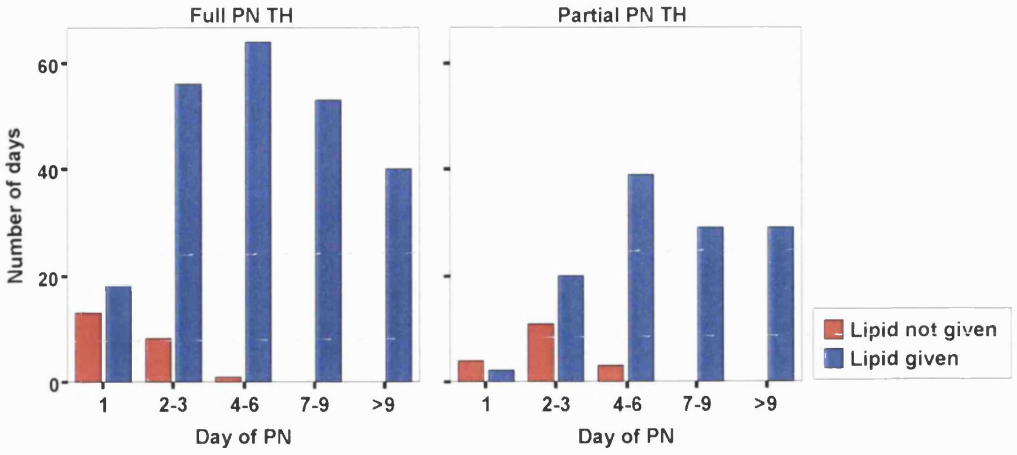

Figure 4.10: Number of days when lipids were administered in TH depending on concurrent enteral feeding

Figure 4.11 shows that in ITH, intravenous lipids were provided independently of enteral intake, and they were more likely to be provided at later stages of PN.

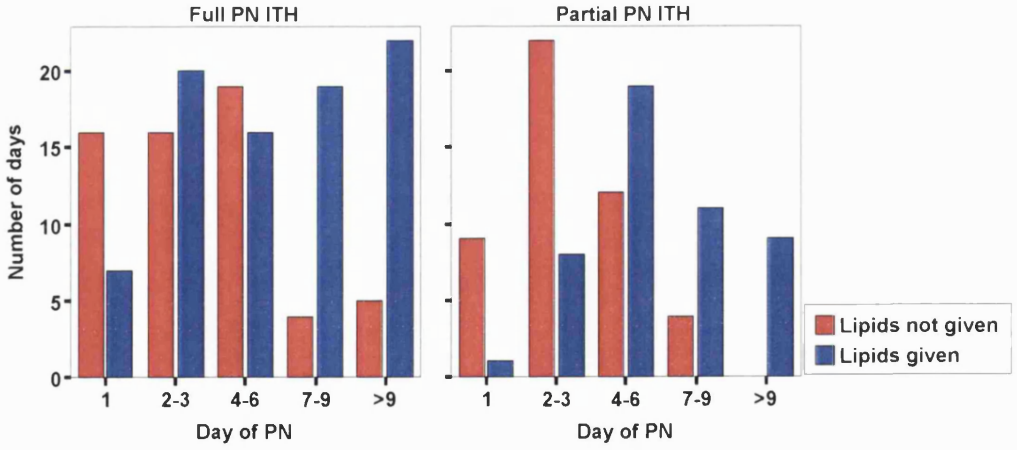

Figure 4.11: Number of days when lipids were administered in ITH depending on concurrent enteral feeding

4.3.7. Enteral feeding

The volumes of enteral feeding given concurrently to PN was recorded. Enteral feeding was administered on 99 days (84%) in GH, on 227 days (57%) in TH, and on 113 days (47%) in ITH. In GH, enteral feeding was given as maternal breast milk on 93 days (94%), compared to TH where maternal breast milk was given on 178 days (78%). In ITH, enteral feeding was given as maternal breast milk on 90 days (80%). The use of enteral nutrition was analysed in more detail in surgical patients in TH and ITH. Table 4.24 shows that significantly less enteral feeding was given to surgical patients. Values shown refer to the full course of PN, not just days before and after a surgical procedure.

kcal/kg/day	Enteral nutrition intake		$\chi 2$	P
	N	Mean ± SD		
Surgical	208	4.4 ± 9.1	75.9	0.000
Non-surgical	543	13.6 ± 16.9		

Table 4.24: Energy from enteral feeding administered in TH and ITH depending on surgery

4.3.8. Prescribed versus administered parenteral nutrition

In order to fully discuss nutritional intake, it is important to know how much of prescribed PN was actually administered to the patient. Disruption to intravenous infusion of PN had various clinical causes, *e.g.* blockage of lines, surgical procedures, deterioration of clinical condition, or the requirement to use more of the available amount of fluid for medication. Specific reasons were not researched for each day when the amount administered differed from the amount prescribed. Sometimes more than the prescribed amount of PN was administered (up to 178% on one occasion). Figure 4.12 shows that, on average, more than 80% of prescribed amounts were administered.

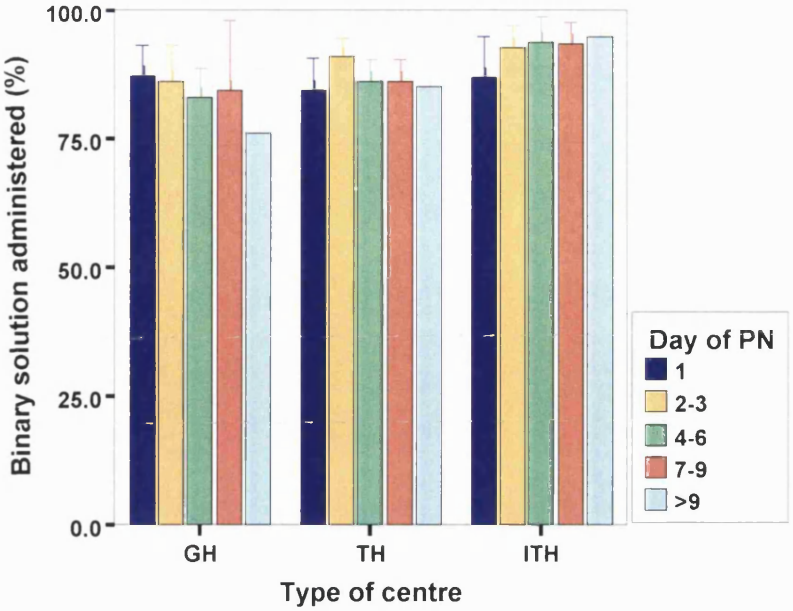

Figure 4.12: Percentage of administered amounts of binary solution versus prescribed amounts

Table 4.2 shows a more detailed breakdown of the number of days when different percentages of binary solution were administered, and it shows that on a substantial number of days less than 80% of the prescribed amounts were administered in GH and TH.

Administered versus prescribed binary solution	GH (N=118)		TH (N=395)		ITH (N=239)	
	N	%	N	%	N	%
>105%	4	3.4	27	6.8	3	1.3
95-105%	33	28.0	137	34.7	169	70.7
80-95%	40	33.9	111	28.1	34	14.2
50-80%	34	28.8	101	25.6	21	8.8
<50%	7	5.9	19	4.8	12	5.0

Table 4.25: Volumes of binary solution administered versus prescribed

In ITH, the compliance to the prescription is much greater with over 70% of days falling into the 95-105% group. The picture is very similar for the administration of lipid emulsion, as shown in Table 4.26.

Administered versus prescribed lipid emulsion	GH (N=68)		TH (N=355)		ITH (N=132)	
	N	%	N	%	N	%
>105%	16	23.5	57	16.1	8	6.1
95-105%	19	27.9	136	38.3	93	70.5
80-95%	19	27.9	102	28.7	14	10.6
50-80%	11	16.2	43	12.1	12	9.1
<50%	3	4.4	17	4.8	5	3.8

Table 4.26: Volumes of lipid emulsion administered versus prescribed

4.3.9. Fluid intake

PN and EN were only one part of total amounts of fluids administered. Other intake included medication and clear fluids. In order to find out more about the role of PN in neonatal fluid management, total daily intake was recorded. It has to be pointed out that data collection only took place if neonates received more than half of nutrition from PN; therefore data will be biased towards a higher level of nutrition from PN compared to the overall neonatal population. Average amounts of fluids administered in GH are summarised in Figure 4.13. Smaller neonates were given more fluids overall and more non-nutritional fluids.

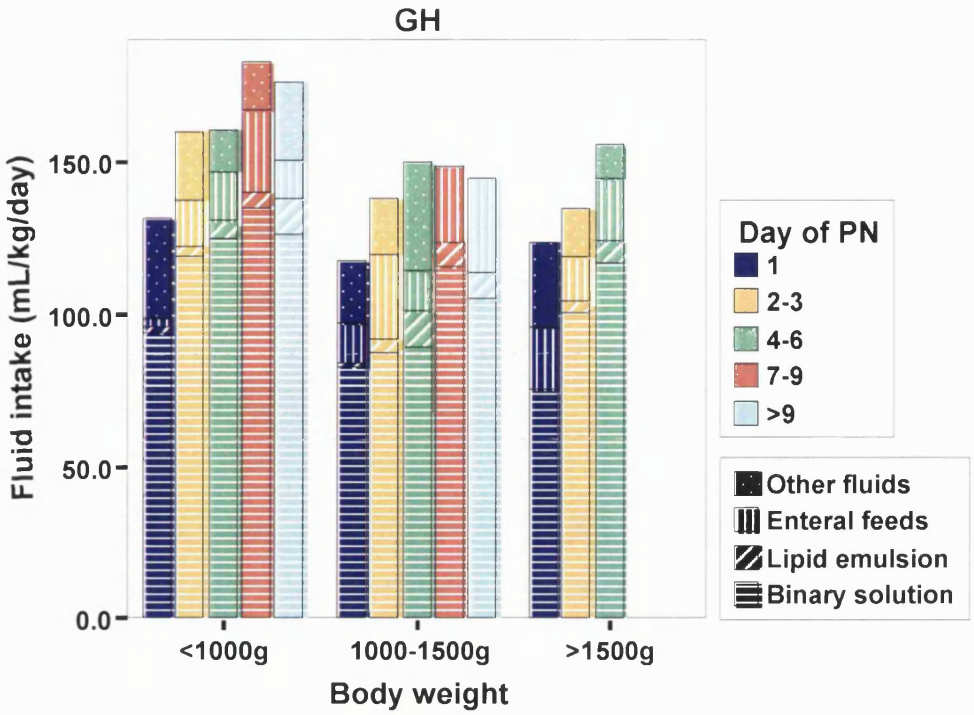

Figure 4.13: Mean fluid intake in GH from binary solution, lipid emulsion, enteral feeds, and other fluids

Fluid intake in TH is shown in Figure 4.14. There was not a great difference between the weight groups regarding total fluids administered, but there was a small tendency to higher non-nutritional fluid intake.

Fluid intake was different in ITH compared to the UK (Figure 4.15). Non-nutritional fluids were given at a higher percentage of total fluids.

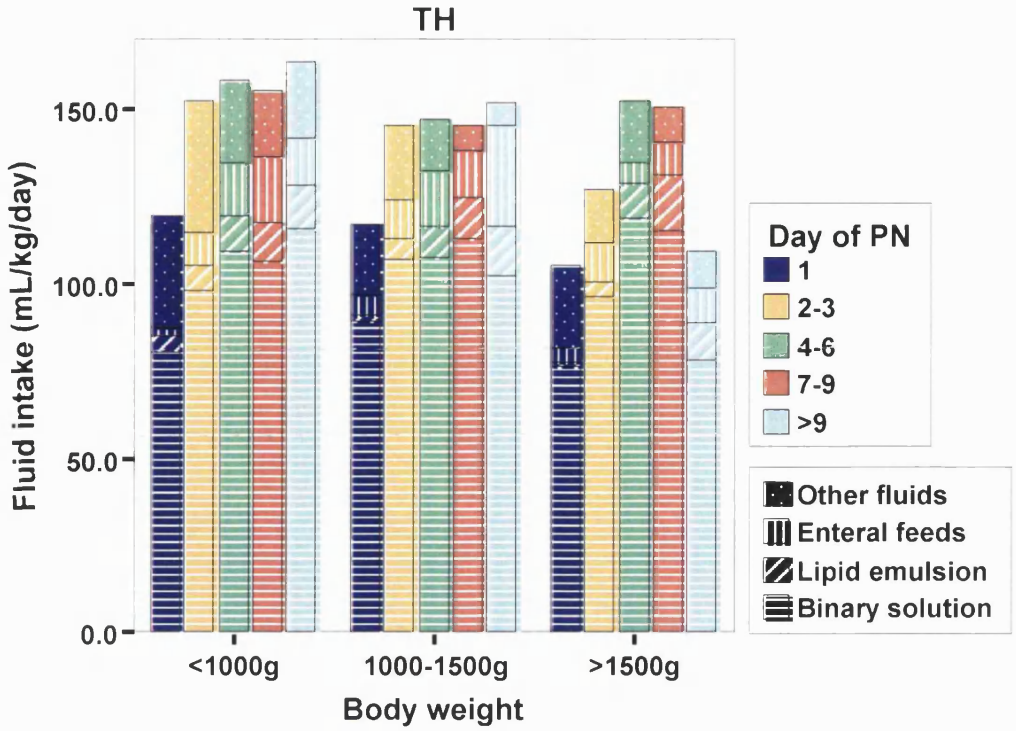

Figure 4.14: Mean fluid intake in TH from binary solution, lipid emulsion, enteral feeds, and other fluids

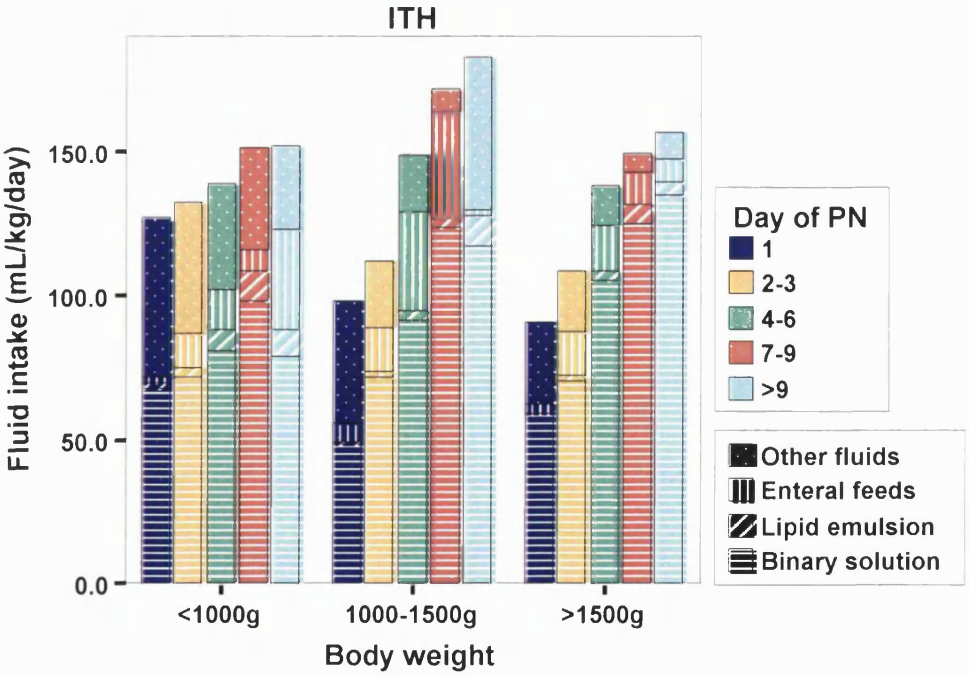

Figure 4.15: Mean fluid intake ITH from binary solution, lipid emulsion, enteral feeds, and other fluids

4.3.10. Total macronutrient intake

In Table 4.27, Table 4.28, and Table 4.29, daily amounts of macronutrient administered from both enteral and parenteral feeding were combined for GH, TH, and ITH respectively. Estimations of breast milk and enteral formulae contents are discussed in the methods section. Although both enteral and parenteral feeding were taken into consideration, intake of macronutrients in GH was lower than prescribed amounts of PN alone (Table 4.27). The average amino acid intake was below 2 g/kg/day, but average lipid intake was reached 3 g/kg/day after nine days of PN.

GH	1st Day	2nd-3rd Day	4th-6th Day	7th-9th Day	>9th Day
(per kg/day)	N=26	N=45	N=29	N=8	N=10
Amino acids (g)	0.9 ± 0.5	1.5 ± 0.5	1.9 ± 0.4	1.6 ± 0.5	1.7 ± 0.6
Glucose (g)	9.3 ± 3.4	12.0 ± 3.7	13.7 ± 2.8	15.0 ± 4.1	12.6 ± 2.7
Lipids (g)	0.8 ± 0.9	1.4 ± 1.2	2.1 ± 1.4	2.5 ± 1.8	3.0 ± 1.6

Table 4.27: Total macronutrient intake in GH (enteral and parenteral feeding)

In TH, amino acid intake reached 2.6 g/kg/day after nine days of PN (Table 4.28). Intake was overall very variable.

TH	1st Day	2nd-3rd Day	4th-6th Day	7th-9th Day	>9th Day
(per kg/day)	N=37	N=95	N=107	N=82	N=69
Amino acids (g)	1.2 ± 0.6	1.9 ± 0.7	2.2 ± 0.8	2.3 ± 0.6	2.6 ± 0.8
Glucose (g)	8.2 ± 3.3	10.6 ± 3.2	12.6 ± 3.8	13.2 ± 4.3	13.4 ± 3.6
Lipids (g)	0.6 ± 0.7	1.5 ± 1.0	2.3 ± 1.2	3.0 ± 1.3	3.2 ± 1.1

Table 4.28: Total macronutrient intake in TH (enteral and parenteral feeding)

Results were similar in ITH, but fewer lipids were given than in TH (Table 4.29).

ITH	1st Day	2nd-3rd Day	4th-6th Day	7th-9th Day	>9th Day
(per kg/day)	N=33	N=66	N=66	N=38	N=36
Amino acids (g)	0.9 ± 0.5	1.6 ± 0.7	2.3 ± 0.8	2.7 ± 0.7	2.7 ± 0.5
Glucose (g)	6.6 ± 2.9	9.8 ± 3.9	13.4 ± 4.8	15.3 ± 4.2	15.1 ± 5.4
Lipids (g)	0.3 ± 0.4	0.9 ± 0.9	1.6 ± 1.5	1.9 ± 1.2	2.0 ± 1.3

Table 4.29: Total macronutrient intake in ITH (enteral and parenteral feeding)

4.3.11. Energy intake

Total energy intake can be estimated from enteral and parenteral macronutrient intake using the conversion factors described in the methods section (4.2.8). Figure 4.16 shows how much energy was given to neonates in the three types of hospitals in the form of amino acids, glucose, and lipids. Intake was lower in ITH than in GH and TH during the first few days of PN. The average energy intake at later stages of PN is very similar in all three types of hospitals at around 80-90 kcal/kg/day.

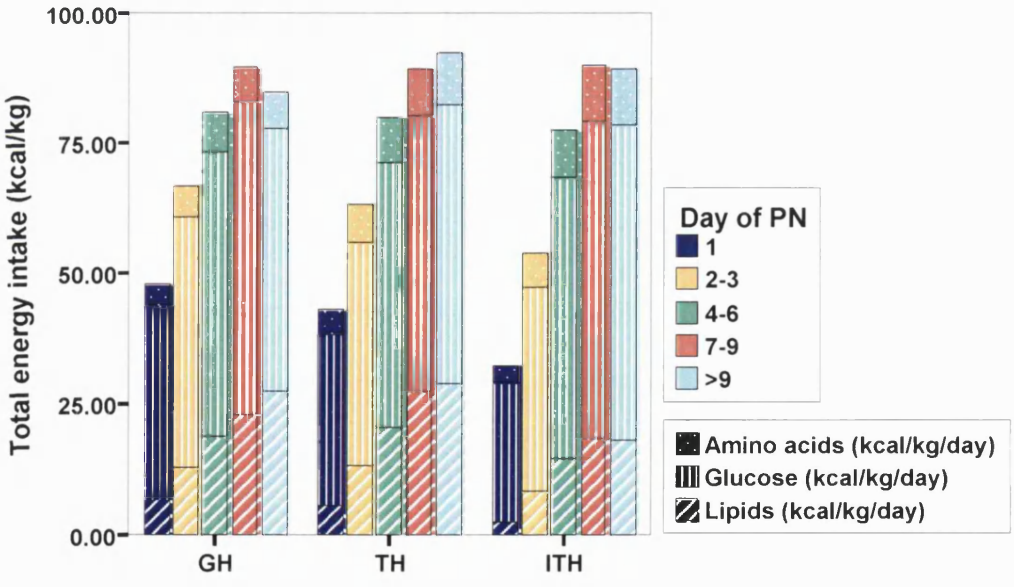

Figure 4.16: Total energy administered from parenteral and enteral feeding

Below, energy intake is shown divided into the three weight groups (Figure 4.17-Figure 4.19).

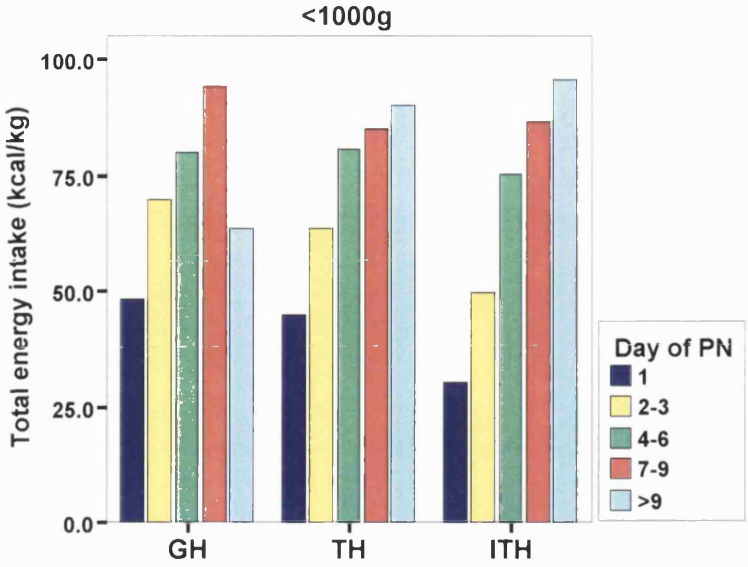

Figure 4.17: Total energy intake from EN and PN per day in neonates < 1000 g body weight

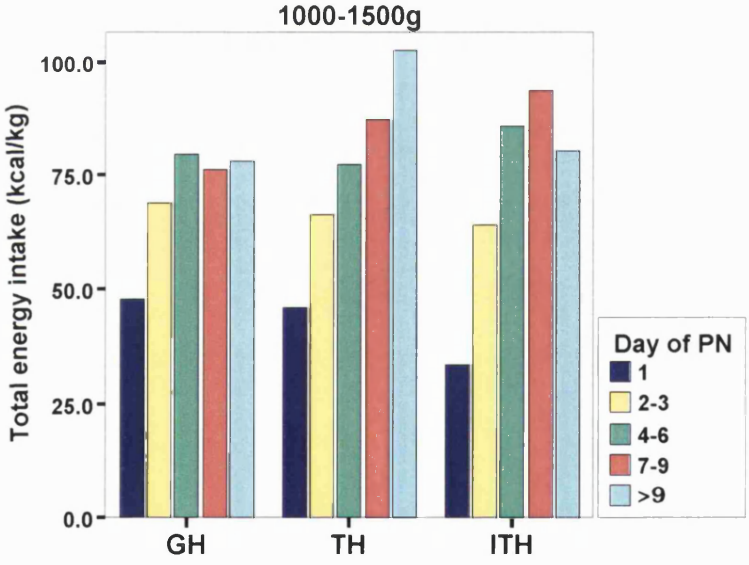

Figure 4.18: Total energy intake from EN and PN per day in neonates 1000-1500 g body weight

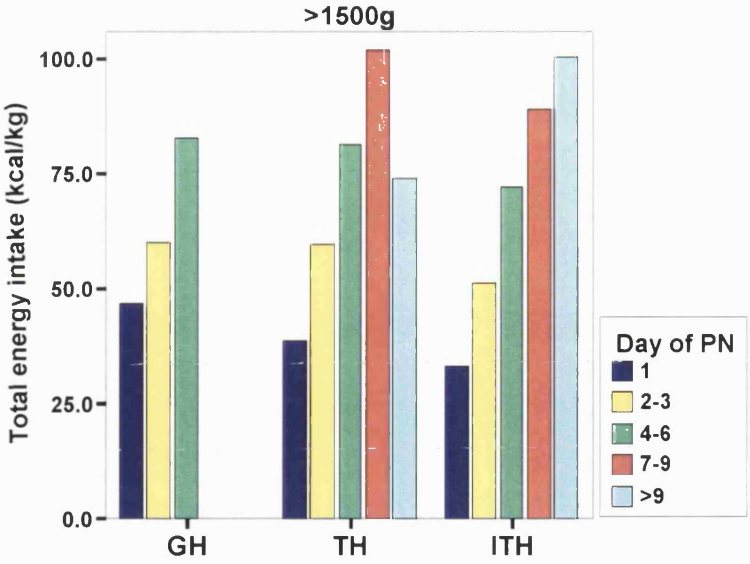

Figure 4.19: Total energy intake from EN and PN in neonates > 1500 g body weight

4.3.12. Comparison of energy intake with recommended intake

Total daily intake of energy was compared with recommended intake for each neonate. As true measurement of energy requirements (*i.e.* measurement of energy expenditure at the bedside) had not been undertaken, several estimations and simplifications had to be made:

1) Calculations were based on body weight only
2) Gestational age was not taken into consideration for the calculation
3) Other clinical factors, such as sepsis, surgery, ventilation or critical illness, were not adjusted for
4) Enteral and parenteral requirement were not considered separately (parenteral requirement are slightly lower, as energy is not required for digestion)[3]

Nearly all neonates were premature (94%) and calculations of energy requirements were based on published recommendations for premature infants.[1] These recommendations state that stable premature infants should be given 100-120 kcal/kg/day to. The lower end of this guideline was used (i.e. 100 kcal/kg/day), to show 'worst case scenario'.
It is important to point out that the following figures have to be considered taking the simplifications above into consideration.
Data are shown as energy deficits per kg per day (Figure 4.20-Figure 4.22).

Figure 4.20 shows how the deficit in energy intake decreases with increasing age in neonates weighing less than 1000 g. After ten days of life, the daily energy deficit ranges from 20 kcal/kg in GH to less than 10 kcal/kg in ITH.

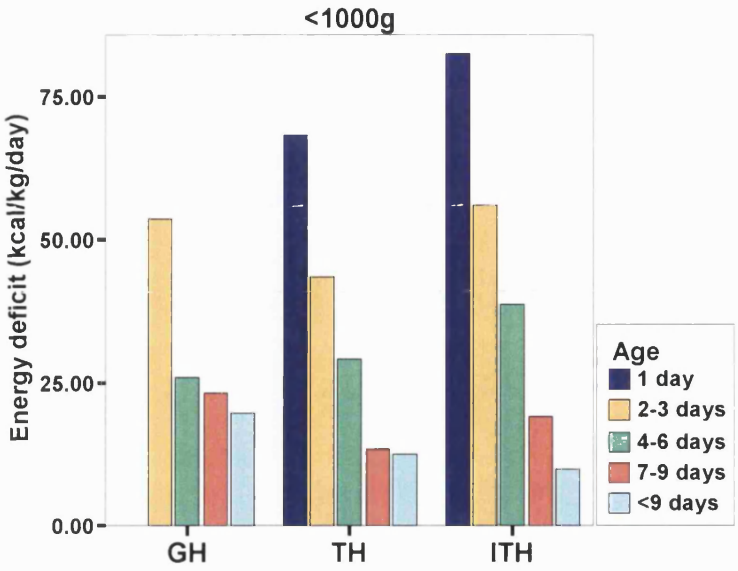

Figure 4.20: Energy deficit (kcal/kg/day) in neonates <1000 g body weight

Neonates weighing between 1000 and 1500 g showed a similar pattern of reduction in energy deficits, but it is interesting to note that in GH and ITH the deficit increased again after the first week of life (Figure 4.21).

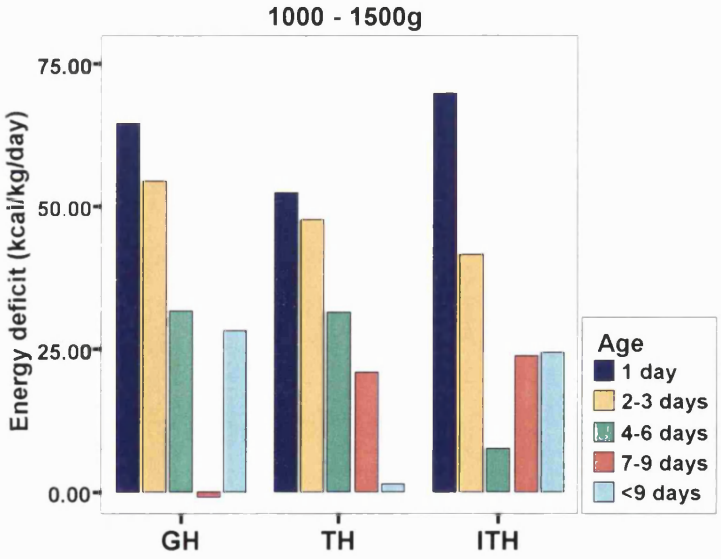

Figure 4.21: Energy deficit (kcal/kg/day) in neonates 1000-1500 g body weight

For neonates weighing more than 1500 g a similar development in energy balance can be seen (Figure 4.22). Data were not available for the first day of life and after nine days of life in GH.

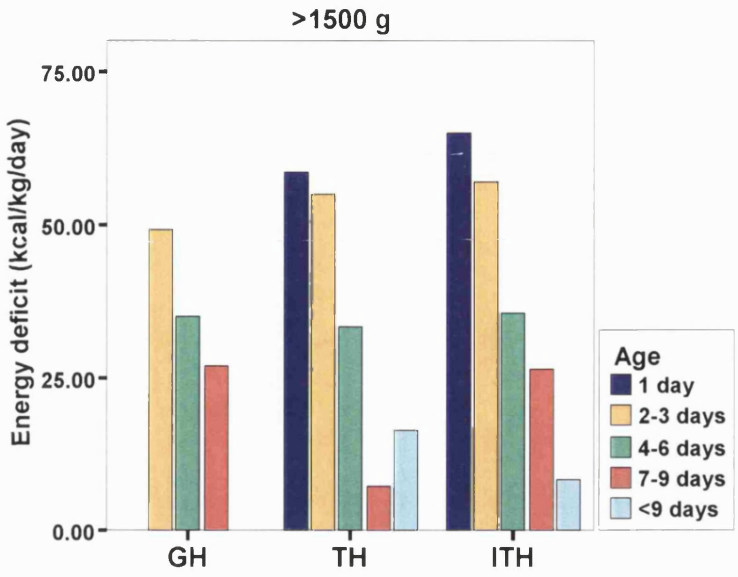

Figure 4.22: Energy deficit (kcal/kg/day) in neonates >1500 g body weight

4.3.13. Weight gain during the course of the study

The last section showed that, on most days of PN, neonates were given less than the recommended energy. In order to find out if this had an effect on overall weight gain, the body weight of neonates was analysed over the course of the study. Figure 4.23 shows how the average weight change was distributed in the three different weight groups (outliers are not shown) (for explanation of boxplot parameter see section 3.3.6).

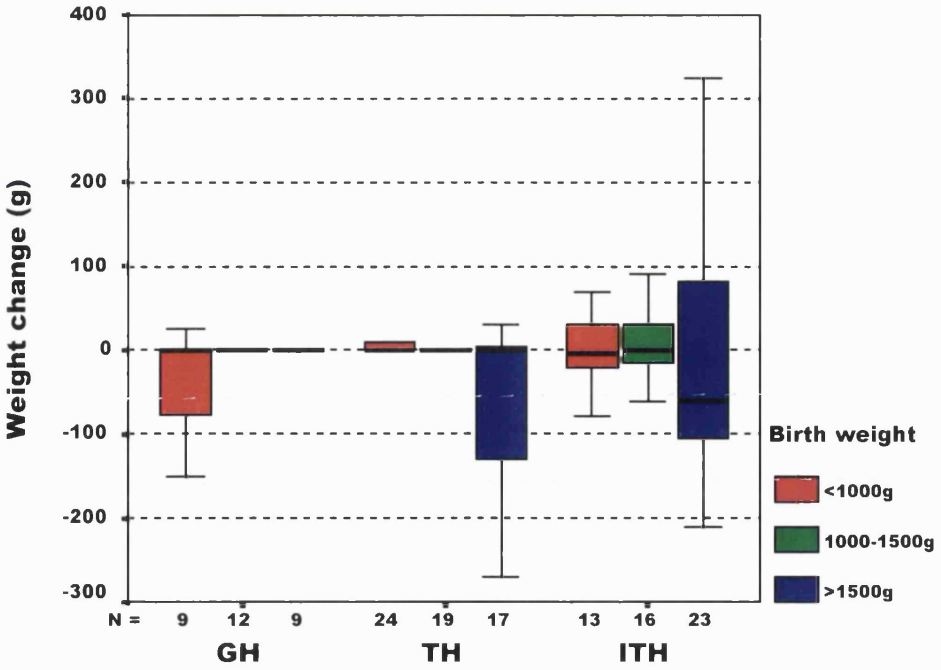

Figure 4.23: Changes in average body weight (g) in the three types of hospitals and for three different birth weight groups

In GH, no weight change was on average observed. Neonates weighing less then 1000g showed a trend of weight loss of 80-120g. In TH and ITH, infants >1500g showed a weight loss trend. Weight change for infants <1500g was minimal in both TH. In ITH on the other hand, infants <1500g showed a relatively wide distribution of both weight gain and weight loss.

Although this comparison of weight gain is a useful indicator of trends, this data has to be viewed with caution. Neonates were enrolled into the study at different points in their first month of life, and data for each neonate were collected for any length of time (from one to fourteen days). The medians and interquartile ranges in the figure above thus do not represent weight change on a homogenous time scale. Additionally, neonates were not weighed every day. As a result, a lack of weight change in some cases might be related to a lack of up-to-date information.

4.3.14. Ratio of amino acids and energy intake

Amino acids can only be utilised efficiently by the body if adequate energy is provided in the form of carbohydrates or lipids.[22] Non-protein energy intake for neonates in this study was always above the recommended ratio (Figure 4.24).

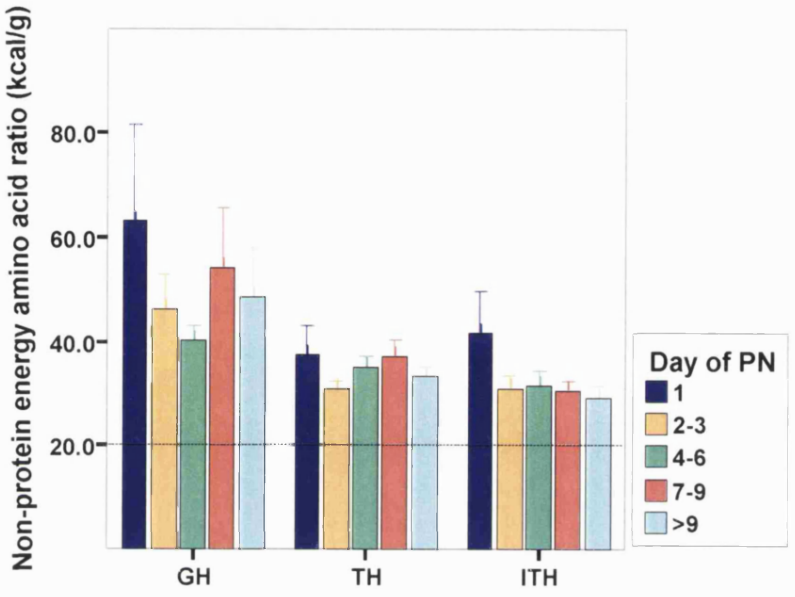

Figure 4.24: Non-protein energy and amino acid ratio (reference line represents minimum recommended ratio)

4.3.15. Use of standard solutions

Standard PN was used in half of the centres included in this study. Of those, four centres exclusively used StSol, whereas the other hospitals use StSol in combination with individualised PN.

StSol were used on 42% of all PN days studied. In the three types of hospitals, the use of StSol was distributed as follows: GH 39 of 118 PN days (33%), TH 212 of 395 days (54%), and ITH 63 of 239 days (26%). Standard PN and non-standard PN were compared in terms of prescribed amounts of macronutrients and total energy intake (Table 4.30).

Prescribed macronutrients per kg per day	Non-standard		Standard		Kruskal-Wallis	
	N	Mean ± SD	N	Mean ± SD	$\chi 2$	*P*
Amino acids (g)	438	2.0 ± 0.8	314	2.1 ±1.0	0.0	0.853
Glucose (g)	438	12.4 ± 4.2	314	11.6 ± 3.4	6.4	0.011
Lipid (g)	315	2.0 ± 1.1	239	1.7 ± 1.0	10.7	0.001

Table 4.30: Comparison of prescribed macronutrients and total energy intake between standard PN and non-standard PN in all hospitals

Amino acid prescriptions did not differ significantly between the two groups, whereas glucose and lipid prescriptions were significantly lower in the standard group.

4.3.16. Intravenous lines

As part of the study the types of intravenous line used to administer the binary solution was investigated. Lines were classified as either having the tip in a central vessel or in a peripheral vessel. The location of line entry into the body was not recorded.

Type of line	GH (N=118)		TH (N=395)		ITH (N=239)	
	N	%	N	%	N	%
Central line	59	64	141	78	140	59
Peripheral line	33	36	39	22	99	41
No information	26	-	215	-	0	-

Table 4.31: Frequency of central and peripheral catheter use for PN administration

It is evident from Table 4.31 that central lines were used most frequently. It is important to note that many data are missing from UK hospitals. The nature of data collection was retrospective and medical records and fluid charts did not always provide information about the type and location of lines used to administer PN. In ITH, data collection was prospective, and no data are missing. Peripherally located lines were more often used in ITH.

4.4. Discussion - Methodology

This study allowed a comparison of prescribing practice in ten UK hospitals and six European hospitals by means of an audit. It offered insight into nutrition management for neonatal patients in the UK and in Europe.

The following critical considerations of the methodology have to be highlighted:

1) Hospitals in the UK were included based on their response to an initial invitation. This inclusion method can have the disadvantage of response bias. Responding hospitals might have been more likely to have a special interest in neonatal nutrition. It is therefore possible that results from these hospitals might reflect better than average practice.

2) Within the UK, one monitor collected data retrospectively, whereas in Europe prospective data collection took place by monitors in each centre. In order to minimise potential diversification of collected data, standard protocols and data collection forms were used, and monitors were personally instructed in the use of the study documentation. An electronic data collection tool was also used to minimise data transcription errors.

Although these measured have been implemented, the comparison between retrospectively and prospectively collected data has to be undertaken with care. Prospective data collection had the advantage that the data collectors did not have to rely on medical notes, but were able to check prescribed and administered nutrition at the bedside. On the other hand, prospective data collection could have introduce bias into the way PN was prescribed and administered, as medical, nursing, and pharmacy staff was aware that the audit was taking place.

Retrospective data collection had the advantage that practice was unbiased, and that data collection time was greatly reduced. On the other hand, all information had to be extracted from notes, which meant that clarification of, for example catheter locations, was not possible. This was particularly true in cases were neonates had already been discharged by the time data were collected.

In conclusion, differences between GH/TH and ITH have to be interpreted taking these limitations into consideration.

In order to reduce differences between UK and ITH data collection, it would have been advisable to choose either retrospective or prospective data collection and not both.

3) Data were collected for a maximum of 15 days per neonates, in order to reduce the risk of weighing data towards a small number of patients. This meant that the study was not able to investigate long-term PN practice in neonates. In order to capture long-term

PN, a separate study needs to be undertaken, which focuses only on neonates receiving PN for more than a fortnight.

4) This study evaluated PN practice for 142 neonates, and 752 nutrition days were analysed. Many subgroups had to be analysed, for example for differing weight, nutrition days, or clinical conditions. This meant that in some subgroups only one or two patients were represented. In conclusion, the overall number of nutrition days was large, but taking the subgroups into consideration, the sample size was relatively small. Extrapolation of results has to take this limitation into consideration.

4.5. Discussion - Results

This study has investigated prescribed PN, administered PN, EN, total fluids, and StSol in neonatal patients. Different types of hospitals in the UK and Europe were included in order to obtain information from a large population of patients. Between centres, neonates did not differ significantly in birth weight, gestation, or Apgar scores; therefore differences in prescribed nutrition and nutritional intake were likely to reflect true differences in prescribing practice. Most neonates were born prematurely and many were small for gestation (Figure 4.1). Surgical neonates in TH and ITH were analysed separately.

PN was usually initiated on the second or third day of life, independent of birth weight. It has been recommended that, if clinically possible and indicated, PN should be started on the first day of life in preterm infants.[1] Several explanations are possible for the slight delay in commencing PN found in this study (Figure 4.2). Due to the way in which data were collected, the next day of life commenced at midnight. Neonates born in the evening, who received PN the next morning, were classified as having received PN on the second day of life, even though PN was given within 24 hours of birth. In many cases, PN might not have been indicated immediately after birth, for example if difficulties in enteral feeding only became apparent after several days.

One of the objectives of this study was to explore the diversity of prescribing practice. Volumes of binary solution prescribed were variable, but there was a steady increase over the first six days, ranging from around 80 mL/kg/day on the first day of PN to 130 mL/kg/day at later stages of PN (Table 4.5-Table 4.7). Overall, prescribed volumes were lower in ITH, reaching only 114 mL/kg/day after nine days of PN.

A decrease in the volume of binary solution was observed at seven to nine days of PN in TH. This was most likely related to an increased volume of concurrent enteral feeding. Table 4.8 shows that differences between the three types of hospitals were significant on the majority of days. In ITH prescribed volumes of binary solution were significantly lower compared with GH and TH until day seven of PN. Prescribed amounts of amino acids in TH were significantly higher in TH compared with GH and ITH.

Volumes of binary solution prescribed depended on the patients' fluid balance, on enteral feeds, and on other fluids administered, for example as diluents for intravenous medication. Fluid balance depends on the infant's maturity, medication, and external factors such as phototherapy or incubators.[12] It is therefore not surprising that prescribed volumes of binary solutions were variable. Differences seen between the three types of

hospitals are probably related to differences in the way fluid balance was managed. The largest difference in prescribing practice can be seen in amounts of amino acids prescribed. Current recommendations for amino acid intake for term infants is 2.5 g/kg/day and up to 3.9 g/kg/day for infants weighing less than 1500 g.[1] Mean birth weight of infants in this study was 1459 g, and many of them could have been expected to have amino acid requirements of up to 3.9 g/kg/day, especially those who were small for gestation. The highest average amount of amino acids prescribed in GH was 2 g/kg/day. Additional amino acids were administered via the enteral route, but analyses of total intake shows that this reached a highest average 1.9 g/kg/day. A recent review of nutrition support of very-low-birth weight infants recommends that 2.5 to 3 g of amino acids should be administered from the first day of PN.[142] Although more than this level of amino acids were prescribed and administered in TH and ITH, the levels were still below current recommendations. The relatively low amounts of prescribed amino acids in this study might be a result of earlier concerns that high amino acid intake by infants might cause metabolic disturbances.[144] Recent studies have however shown that intakes of 3.5-4 g/kg/day are safe even in extremely low-birth-weight infants (<1000g).[31,141]

Prescribed and administered amounts of glucose were similar across all hospital types. Recommended intake for premature infants is 14-18 g/kg/day, but it depended on metabolic tolerance. Insulin can be used to control hyperglycaemia in infants in order to ensure sufficient energy intake.[1,32] The use of insulin has not been recorded in this study, but it appears that prescribed amounts of glucose were within current recommendations and were typically given in sufficient amounts to allow effective nitrogen retention.

Lipids form an important part of PN, especially if enteral feeds are not provided. Lipids are not only a highly caloric source of energy; they also provide essential fatty acids. The recommended intake for infants is 0.5-1.0 g/kg/day on the first day, followed by progressive increase to 3 g/kg/day. Essential fatty acid deficiency can be avoided with 0.5 g/kg/day.[145] Highest amounts of lipids prescribed were 2.2 - 2.6 g/kg/day, but on many days no lipids were prescribed at all, especially during the first three days of PN. Lipids were prescribed most readily in TH, and lipids were part of the prescription on the first day of PN on twenty out of thirty-seven days. Highest total intake of lipids could also be seen in TH, where average intake reached 3.2 g/kg/day after nine days of PN.

Data were further analysed to take into account that prescriptions might have differed for different groups of infants (Table 4.9-Table 4.11). Literature recommendations differentiate between amino acid needs of infants < 1500 g and term infants (3.5 versus 2.5 g/kg/day),[1] whereas recommended intake for glucose and lipids are similar for both groups. In this study, body weight did not appear to be a reason for differences in PN prescriptions. Only a slight tendency to prescribe more amino acids to smaller infants could be identified in TH and ITH.

The effect of body weight on prescribing practice was further analysed by one-way analysis of variance (Figure 4.3-Figure 4.8). In the previous section (4.3.3), body weight and day of PN had been considered separately. Analysis of variance enabled the comparison of both factors at the same time, *i.e.* are neonates of different body weight prescribed nutrients differently during the progression of PN? Analysis of variance could, for example, detect, whether smaller neonates are first prescribed less macronutrients, but then, after several days of PN, are prescribed more than neonates weighing more then 1500g. This analysis gave a graphical display of the relationship and also an analysis of statistical significance.

Amino acid and lipid prescriptions did not change significantly with body weight. There was, however, a significant interaction between day of PN and body weight in both TH and ITH for glucose prescriptions. In TH, neonates weighing more than 1500 g were prescribed more glucose than smaller neonates between days four and nine, but less on days one to three and after nine days. In ITH, neonates below 1500 g were prescribed similar amounts of glucose, but neonates weighing more than 1500 g were initially prescribed less, and then, after four to six days, more glucose than smaller neonates. It is possible that this was related to an accelerated glucose tolerance in more mature neonates.

It had been estimated that macronutrients in PN prescriptions would be increased if no concurrent enteral feeding were given. In GH and TH, prescriptions did not differ for neonates on full or partial PN (Table 4.12 and Table 4.13). In ITH, however, significantly more amino acids were prescribed to neonates on full PN until nine days of PN (Table 4.14). On some days, more glucose was prescribed, but lipid prescriptions were not affected by enteral feeding.

A fifth of neonates in TH and a quarter of neonates in ITH had undergone surgery. Separate analyses of PN prescriptions in this group of patients showed consistently

higher amounts of prescribed macronutrients, particularly lipids (Table 4.15). These results are not surprising, as metabolic studies have found that increased lipid provision reduce the CO_2 load compared to equivalent amounts of energy from glucose.[146] This might be particularly important in infants suffering from respiratory problems. Overall energy requirements have not been found to be increased in surgical infants.[138] In TH, surgical infants were significantly more mature at birth than non-surgical infants. Differences in prescribed amounts of macronutrients might therefore be related to the increased maturity and not to the surgical procedure itself. However, this is unlikely, as this study has shown that prescriptions did not differ greatly for neonates of different weight.

It is important to note that overall neonates were grouped as surgical patients, and all their nutrition days were analysed as surgical days, *i.e.* pre- and post surgical days. It is possible that small nutritional differences between surgical and non-surgical neonates can only be detected if post-surgical days are specifically investigated.

Prescribed macronutrients and total energy intake were compared for neonates who received StSol and then compared to those who received individually prescribed and compounded solutions. Amino acid prescriptions did not differ significantly, but amounts of glucose and lipids were lower in the group receiving StSol. This is an important finding that highlights the fact that the use of StSol must be investigated thoroughly in order to ensure that nutritional intake in not compromised.

Prescribed amino acids and glucose were also converted into concentrations in order to compare findings in this study with an empirically derived StSol, with literature reports, and with results from earlier work during this project.

Comparison of prescribed macronutrients with a theoretical standard showed that agreements between the two were very low (Table 4.19-Table 4.23).

As previously mentioned, comparison of actual prescribing practice with an empirical StSol was based on a pilot study undertaken by Beecroft and colleagues.[143] They investigated how often prescribers deviated from computer software recommendations. Results showed that 82% of prescription deviated from computer recommendations. Changes were most frequently made to amounts of glucose, sodium, and phosphate. Beecroft and colleagues conclude, however, that, with suitable adjustments to the computer recommendations, up to two-third of all prescriptions could be met by a limited range of StSol. These adjustments were mainly related to increased carbohydrate, sodium, and phosphate prescription, which indicates that the original

computer guidance were not suitable. Computer recommendations for phosphate were, for example 1mmol/kg/day, which frequently lead to hypophosphataemia.
In contrast to Beecroft and colleagues findings, this present study found that macronutrient prescriptions deviated greatly from an empirically derived StSol. Prescriptions were usually for lower amounts of macronutrients compared to the StSol. This disagreement requires further investigation, especially with regard to the clinical feasibility of using the higher concentrated formula.

This study has also shown that prescribed PN volumes were variable and differed greatly between the three types of hospitals. Hospitals previously surveyed (chapter 3 of this thesis) reported that their StSol contained 1.2-1.7 g/100 mL amino acids and 10-12.5 g/100 mL glucose. Suggestions for potentially suitable neonatal StSol were on average higher for both amino acids (2.5 g/100 mL) and glucose (14 g/100 mL). Literature reports show that neonatal StSol often contained 10 g/100 mL glucose and amino acid concentrations that ranged from 1.8 g/100 mL to 2.6 g/100 mL.[102,105] This study has shown that, in GH, mean amino acid concentrations were very similar to those reported in the literature, ranging from 1.2-1.6 g/100 mL. Average concentrations in TH reached 2.7 g/100 mL and in ITH 3.1 g/100 mL. Similarly, mean glucose concentrations in GH were 8.4-12.4 g/100 mL in GH, 9.3-15 g/100 mL in TH, and 10.5-14.5 g/100 mL in ITH. Higher concentrations of amino acids in ITH are related both to larger amounts of amino acids and reduced volumes of binary solution prescribed.
This comparison of results from the survey (chapter 3 of this thesis) with prescribed amounts of macronutrients and PN volumes highlights the fact that the introduction of StSol needs to take individual hospitals' prescribing practice and fluid management into consideration in order to ensure that sufficient amounts of nutrients are provided.

This first part of the study investigated prescribed PN and compared prescriptions for neonates of different weight or clinical situation. Prescriptions were also compared for neonates on partial and full PN. In order to obtain a more detailed picture of neonatal clinical nutrition, other factors had to be considered, for example the amount and type of concurrent enteral feeding. It was also considered important to investigate how much total energy and nutrients were administered each day. This was calculated from amounts and type of enteral feeding given and from the amounts of PN administered. Subsequently, this calculation allowed an accurate comparison of nutritional intake with currently recommended intake in the literature.

Enteral feeding was given concurrently with PN on the majority of days in GH and on about half of PN days in TH and ITH. The lower prevalence of enteral feeding in TH and ITH could be explained by the fact that surgical neonates who received less EN were treated in these two types of hospitals. It has been recommended that enteral feeds should be administered concurrently to PN as soon as clinically possible, and as little as 0.5 mL/kg/day has been shown to be beneficial.[1]

In order to measure total PN intake, the difference between prescribed and administered PN was recorded. Previous studies of administered amounts of enteral feeds in adults showed that 61% of patients received more than 75% of prescribed volumes.[147] It is difficult to extrapolate these results to PN in neonatal intensive or special care, but they give an indication that this is an important problem that needs to be recognised when providing special nutrition support. Others investigated adherence to prescriptions in adult intensive care and found that low amounts of initially prescribed nutrition were reduced further by the fact that ten percent were on average not administered.[148] They discovered, however, that insufficiently prescribed amounts of nutrition played a more important role in underfeeding than the discrepancy between administered and prescribed amounts. This study found that in some cases less than 50% of prescribed PN was administered (Table 4.25 and Table 4.26). In those cases, discrepancies between prescribed and administered PN can potentially lead to significant underfeeding. Results from this study show that PN was in most cases administered in satisfactory amounts, *i.e.* more than 80% of prescribed volume. It is, however, important to note that neonates in the UK received less than 80% of prescribed PN on approximately 30% of nutrition days studied. This discrepancy, together with initially low amounts of prescribed macronutrients, might have contributed to a significant under-provision of nutrients in some instances. Although these results can give an indication of the extent of deviation from the prescription, reasons for this have not been investigated. In order to develop recommendations for potential improvements in this area, more detailed prospective studies have to be undertaken.

Total energy intake was very similar in the three types of hospitals (Figure 4.16). Interestingly, energy intake from lipids was lower in ITH than in TH and GH. This was most likely related to the fact that intravenous lipids and enteral feeds were given on fewer days in ITH.

Amino acids can only be utilised efficiently by the body if adequate energy is provided in the form of carbohydrates or lipids.[22] Data extrapolated from animal studies and adult PN patients suggests that 20 non-protein kcal/g amino acids are sufficient for amino acid utilisation.[22] This study found that non-protein energy intake for neonates was always above the recommended ratio (Figure 4.24).

PN can be given through a central or peripheral line. The choice of line depends on the availability of venous access, osmolarity of the solution for infusion, and estimated length of time of line use.[149] Central venous access was mainly used in the population in this study (Table 4.31). A surprising finding during the course of this study was the difficulty in retrospective identification of the type of venous access used in the UK. Neonates' fluid charts did not always specify the type of line used for binary solutions or lipid emulsions. This problem did not arise in ITH, because data collection was prospective. It would appear that the recording of the catheter location forms an important part of documentation in neonatal care, and that this would be important for reasons of accountability and clinical governance.
This means that a comparison between ITH and the other hospitals in the UK is not possible. Furthermore, no detailed definition of 'central catheter' was offered in the study protocol. Hospitals' own interpretation of central and peripheral lines was adopted, as it was not known at the time that differences in interpretation exist. As a result it is, for example, not known whether femoral groin access was considered to be central or peripheral.

5. Optimising intravenous lipid administration for neonatal and paediatric patients

5.1. Introduction

The administration of fatty acids in the form of lipid emulsions is essential in order to provide essential nutrients and high-density calories.[1] Lipid emulsions are typically given in the form of TNA to adult patients. This has been shown to be cost effective and safe, and the stability of these complex emulsions has been thoroughly studied.[56,118,150]
In paediatric patients, however, lipid emulsions are usually given in the form of separate infusions, as highlighted in the preceding two chapters. The reasons for this have been multifactorial including: emulsion stability concerns related to high concentrations of calcium and magnesium,[18] and the historical assumption that TNA would provide an excellent growth medium for microbial contaminants.[118] It has since been shown that TNA supports microbial growth no more than glucose 5% solutions for most nosocomial pathogens.[119] Rollins and colleagues have also shown that TNA can be used safely in infants and that it provides a more cost effective way of administering lipids.[82]
Another reason to give lipids separately has been the concern that calcium phosphate precipitates would not be visible in TNA. Precipitation of calcium phosphate has been of major stability problem in paediatric PN. This issue lead to a safety alert by the Food and Drug Administration, after several death in 1994 were linked to infusion of calcium phosphate particles.[151] Since then, organic phosphates (*e.g.* glucose-1-phosphate, glycerol phosphate, fructore-1,6-phosphate) have become available that allow safe provision of calcium and phosphate in one solutions with a greatly reduced risk of precipitation.[46] It appears that this problem has now been largely addressed.
A more recent concern has been the formation of lipid peroxides in PN. Their detection is discussed controversially, as shown later in section 5.1.4.
This laboratory study was conducted to test whether or not TNA contain less peroxidised lipids than lipid emulsions alone and to thereby provide a new aspect in the discussion surrounding the administration practice of lipids in neonatal and paediatric patients.

5.1.1. Reactive oxygen species

Aerobic organisms derive their energy from the reduction of oxygen, and, in the process, highly reactive oxygen intermediates are formed, *e.g.* $O^{\cdot}{}_2^-$ (superoxide), $OH^{\cdot}$ (hydroxyl radical) and H_2O_2 (hydrogen peroxide). These species, together with unstable intermediates in the peroxidation of lipids, are referred to as reactive oxygen species (ROS).[152] Although $O^{\cdot}{}_2^-$ and H_2O_2 are able to cause cellular damage, they are weak oxidants in aqueous solutions. Their importance with regard to the pathophysiologic role of ROS is that they are substrates in the formation of hydroxyl radicals ($OH^{\cdot}$).[153] Hydroxyl radicals are formed when superoxide and hydrogen peroxide react to generate oxygen and hydroxyl radicals:[154]

$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\cdot} + OH^-$ (Fenton Reaction).

In 1934, Haber and Weiss proposed that superoxide and hydrogen peroxide could react to form the hydroxyl radical:[154]

$O^{\cdot}{}_2^- + H_2O_2 \rightarrow O_2 + OH^{\cdot}$ (Haber-Weiss reaction).

It has since been shown that this reaction is only likely to occur *in-vivo* if transition metals are present to act as catalysts.[154]
The hydroxyl radical is highly reactive and able to react with many organic molecules; thus it plays a pivotal role in causing oxidative damage to *in-vivo* systems.[154]

ROS are part of normal aerobic life, and systems are in place to scavenge those highly reactive substances. Hydrogen peroxide has been shown to play an important part in the formation of hydroxyl radicals. As a result, it is advantageous for *in-vivo* systems to control the amount of hydrogen peroxides present.[154] There are two specific enzymes designed to remove hydrogen peroxides: catalases and peroxidases.[154] Catalase is present in most aerobic cells and inactivates hydrogen peroxides by the following reaction:

$2\ H_2O_2 \rightarrow 2\ H_2O + O_2$.

Glutathione peroxidase is the most abundant of the various peroxidases. The substrate glutathione (GSH) is a simple tripeptide (glutamic acid – cysteine – glycine) that is

present in its oxidised from as a GSH dimer joined with a disulphide bridge (GSSH). Once GSH has been oxidised to GSSH, glutathione reductase catalyses the reaction to reduce GSSH back to GSH.[154]

Another important ROS is superoxide. This species is inactivated by superoxide dismutase. Superoxide is the specific substrate for superoxide dismutase, and the dismutase is most abundant as copper-zinc containing enzyme. Superoxide is inactivated by the following reaction:[154]

$O^{\cdot}{}_2^- + O^{\cdot}{}_2^- + 2H^+ \rightarrow H_2O_2 + O_2.$

Other non-enzymatic molecules are able to protect *in-vivo* structures from damage by ROS. Ascorbic acid is a potent electron donor and plays a role in various anti-oxidative pathways. Its key roles include keeping metal ions in hydroxylase enzymes in the reduced form, detoxifying organic radicals *in-vivo*, and reacting readily with ROS (including superoxide and hydroxyl radicals).[154]

When reduced, ascorbic acid forms semi-dehydro-ascorbic acid and dehydro-ascorbic acid (DHA) (Figure 5.1). Further breakdown of DHA eventually produces oxalic acid.

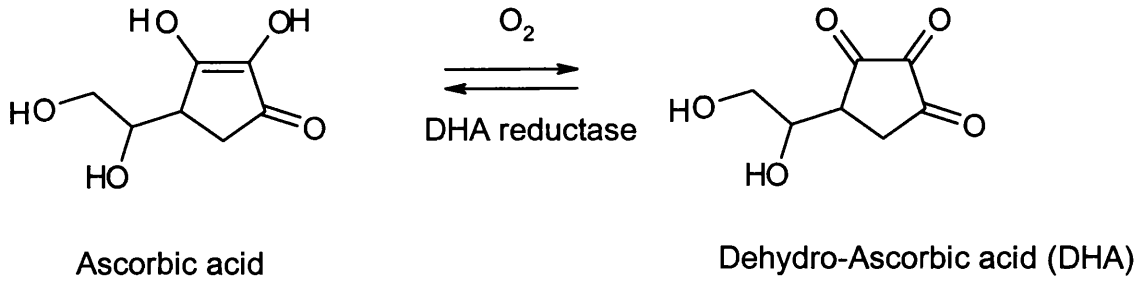

Figure 5.1: Reversible oxidation of ascorbic acid to dehydro-ascorbic acid

In order to prevent the formation of toxic oxalic acid, organisms have evolved systems to revert DHA back into ascorbic acid. The enzyme involved in this process is DHA reductase. Despite these important anti-oxidative properties, ascorbic acid has also been linked to pro-oxidative reactions, such as the formation of hydroxyl radicals via the Fenton reaction.[154] This occurrence is dependent on the concentration of ascorbic acid.

Another non-enzymatic scavenger is GSH. GSH is not only a substrate for glutathione peroxidase, but also a direct scavenger of hydroxyl radicals.[154]

5.1.2. Lipid peroxidation

Lipid peroxidation has been defined as the 'oxidative deterioration of polyunsaturated lipids'.[154] This event can be initiated by hydrogen extraction from a methylene group by hydroxyl radicals.

Conjugated dienes are formed, which then readily take up oxygen to form peroxy radicals (Figure 5.2).

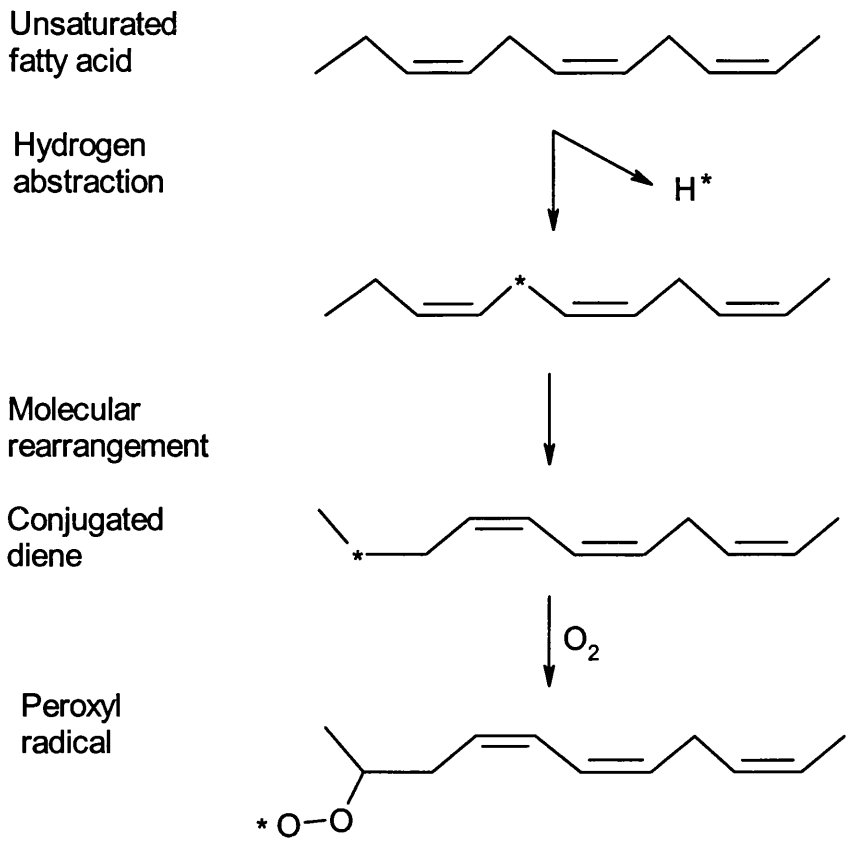

Figure 5.2: Formation of peroxyl radicals from unsaturated fatty acids

This process is called 'first-chain initiation'. Peroxy radicals can then react further by extracting hydroxyl radicals from methylene groups of other fatty acid chains. This chain reaction is called the 'propagation stage' of lipid peroxidation. The process of lipid peroxidation occurs not only in biological membranes, but also in food lipids.[154] The most important antioxidant in the peroxidation of lipids is the chain breaking α-tocopherol (Figure 5.3) (although β, γ and δ-tocopherol also have some antioxidant activity).

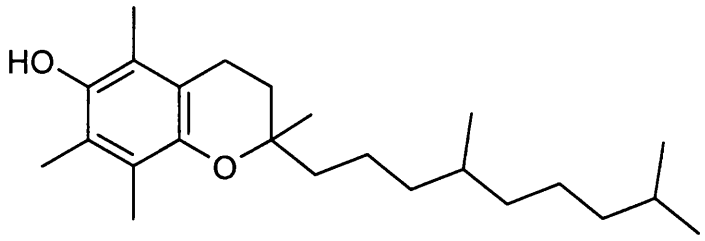

Figure 5.3: Chemical structure of α-tocopherol

Tocopherols are lipophilic substances that are embedded into the structure of biological membranes. They are able to react with lipid peroxy radicals by donating their labile hydrogen and forming the relatively stable tocopheryl radical. In order to reduce the radical back into tocopherol, a synergistic activity by ascorbic acid has been suggested.[154]

5.1.3. Oxidative stress and parenteral nutrition

In-vivo, an imbalance between pro-oxidant and anti-oxidants in favour of the pro-oxidant sometimes occurs. This imbalance is called oxidative stress.[152]

A number of clinical conditions have been linked to oxidative stress including atherosclerosis, multiple sclerosis, solar radiation injury, and rheumatoid arthritis. It has been questioned whether the increased levels of ROS measured in such conditions are primary causes of the disease or if they are secondary effects of cellular damage.[154]

In paediatrics, a number of pathologies have been linked to oxidative stress including necrotizing enterocolitis and retinopathy of prematurity.[153] Premature infants were found to have insufficient levels of superoxide dismutase and vitamin E. As a result, the infants were more susceptible to biological damage from radicals and peroxides.[153]

Wispe and colleagues first examined the role of intravenous lipid emulsions in contributing to oxidative stress in neonates in 1985.[155] These investigators measured exhaled ethane and pentane in newborn infants receiving lipids intravenously and they found that the infusion of lipids increased the amount of expired pentane significantly. Subsequently, they suggested that one possibility for the increase in lipid peroxidation markers could be an increased level of LPO in the lipid emulsion *in-vitro*.

Hammerman and colleagues investigated the effect of lipid emulsions on outcome in premature infants in a randomised trial comparing infants receiving lipids with infants not receiving lipids.[156] They found an increased incidence of retinopathy of prematurity in the lipid group. As a result of this work, they proposed that lipids should be given

with caution during the first week of life. Additionally, they proposed that the increase of pathological events could have been related to prostaglandin-mediated events.

PN can contribute to oxidative stress either due to the peroxides present *in-vitro*, or due to *in-vivo* reactions to the intravenous administration of nutrients. Although it has not been shown directly that the administration of peroxidised PN poses a problem, it is considered undesirable.[67]

Several groups have investigated *in-vitro* formation of peroxides, but it is currently not known which concentrations of peroxides are potentially damaging, nor how easily infused peroxides are scavenged *in-vivo*.[65,157,158] It is also not known how effectively different types of peroxides, *i.e.* lipid and hydrogen peroxides, are scavenged. Although, it has been suggested that hydrogen peroxides are more easily scavenged than lipid peroxides.[66]

In-vivo contribution of PN to oxidative stress is more complex. PN solutions are exposed to an oxygen-rich environment when entering the bloodstream, and as a result susceptible molecules, such as riboflavin and polyunsaturated fatty acids, could potentially be oxidised. Basu and colleagues found that oxidative stress generated by PN in infants could be reduced, by maximising the utilisation of infused lipids through concurrent reduction of glucose intake.[159] Lipid peroxidation is not only important with regard to clinical and toxicological implications, but also with regard to pharmaceutical stability. Peroxidation leads to rancidity of lipids; therefore it is undesirable in terms of overall product quality.[154]

5.1.4. Quantification of peroxides

It is advantageous to know the level of contamination of intravenous lipid emulsions with LPO for several reasons. This knowledge allows assessment of pharmaceutical product quality, enables evaluation of strategies to reduce their formation, and supports the interpretation of *in-vivo* studies of oxidative stress related to PN.

Although the European Pharmacopoeia sets a limit for peroxides in intravenous lipids (see below),[74] the clinical implications of peroxide administration from pharmaceuticals are less clear. Because PN is usually infused in large amounts and sometimes for very long periods of time, it is desirable that the concentration of *in-vitro* LPO is as low as possible.

Various methods have been employed to quantify peroxides *in-vitro*. The European Pharmacopoeia's method of choice to determine the peroxide value (milliequivalents of active oxygen in 1000 g of the substance) is by iodometric titration.[74] The limit for LPO in Soybean oil for intravenous use is 5 mmol/kg oil. This is equivalent to 1 mmol LPO per litre of 20% lipid emulsion. Steger and colleagues adopted this method to determine *in-vitro* oxidation of intravenous lipid emulsions.[160] The main disadvantages of this method were related to the large amounts of solvents required for each sample extraction (50 mL of chloroform and methanol mixture) and susceptibility of iodine to the presence of oxygen. The recovery of extracted LPO was 78% and the detection limit was 20 μM in 20% lipid emulsion. The standard used for comparison was cumene hydroperoxide. Lipid emulsions were stored for four weeks in EVA or polypropylene/polyamide containers for TNA, and LPO values of up to 3 mmol/L lipid emulsions were detected.

Others used the ferrous oxidation – xylenol orange (FOX) method.[66,161] This method measures the absorbance of a complex of ferric ions (which are formed from ferrous ions after oxidation with peroxides) with xylenol orange.[162]

Laborie and colleagues measured peroxides in TNA without prior extraction of lipids.[126] As a consequence, this method did not distinguish between hydrogen and lipid peroxides. Silvers and colleagues have critically evaluated this approach, and they found that the FOX method is susceptible to the presence of ascorbate.[161] The authors concluded that results showing that multivitamin solutions were a major contributor to the peroxide load in intravenous lipid emulsion were questionable. It has also been suggested that reliability of the FOX method is impaired by the fact that molar absorptivity of the ferric-xylenol orange complex vary with different makes of the dye.[163]

Other researchers have used high performance liquid chromatography (HPLC) to quantify LPO.[158] Peroxides oxidise isoluminol in the presence of heme. Isoluminol is then quantified using post-column chemiluminescence. Method validation included the use of triphenylphosphine (TPP), a strong reducing agent, which quantitatively reduced LPO. The authors concluded that the response generated was specific to peroxides. Helbock and colleagues investigated LPO concentrations in freshly opened bottles of 20% lipid emulsions, and found that they contained between 214 and 655 μM LPO.[158] Silvers and colleagues also used this HPLC method to quantify LPO in lipid emulsions

and found that in newly opened bottles LPO levels varied substantially, but were usually below 100 μM.[66]

Various factors, which can potentially influence the formation of peroxides in lipid emulsions, have been investigated in the literature, including natural light and phototherapy light, oxygen exposure, length of storage, different TNA formulae, and different types of lipid emulsions.[120,126,160,161,164-166] Some researchers have also investigated peroxide formation during simulated infusion of lipid emulsions and TNA.[66,126,165,166]

After finding that addition of vitamins reduces the amount of total peroxides and LPO formed, Silvers and colleagues recommended that lipid emulsions should be mixed with multivitamins and administered via dark delivery tubing.[66] In administration tubing exposed to phototherapy, LPO concentration ranged from 20 μM in light protected tubing to 50 μM in light exposed tubing.[66] Total peroxides measured by the FOX method ranged from 120 to 270 μM.

Laborie and colleagues investigated the influence of light protection in more detail, especially with regard to the use of coloured administration tubing.[126] They found that orange and yellow tubing provided suitable protection whilst allowing monitoring of air bubbles.

Lipid peroxidation has been investigated in great detail in biological materials, such as plasma and cell-cultures.[152] Basu and colleagues measured plasma malondialdehyde (MDA) in surgical infants receiving PN.[159] MDA is one degradation product of lipid peroxidation. Basu and colleagues compared plasma MDA concentration generated by two different PN regimens. Firstly, infants were given 3 g/kg/day of lipids and glucose infusion was reduced from 18 g/kg/day to 10 g/kg/day. Secondly, infants received constant amounts of glucose (18 g/kg/day), but lipid infusion of 3 g/kg/day was stopped. Results showed that the first PN regimen promoted lipid metabolism. The authors concluded that reducing glucose lipid ratio reduced reduces free radical formation *in-vivo*.

Other measurement techniques for biological samples include photometric quantification of conjugated dienes or thiobarbituric acid reactive materials and measurement of loss of fatty acids by HPLC.[152] It is also possible to measure LPO *in-vivo* by quantifying exhaled hydrocarbon gases (using gas chromatography) that have formed during the decomposition of LPO.[155]

5.1.5. Evaluation of the ferric thiocyanate assay

Shortcomings were discovered in the methods described in the literature for the quantification of LPO in PN solutions. These methods were either based on complex techniques, such as HPLC with post column chemiluminescence detection,[164] or, in the case of the FOX method, have been criticised for being prone to interferences.[66] Measurement of LPO separately from hydrogen peroxides was also not common practice and required either special HPLC equipment or large quantities of solvents for iodine titration.

It was therefore decided to explore the literature further for novel methods of LPO detection. Measurement of LPO is common practice in investigations related to the *in-vivo* role of free radical damage. The ferric thiocyanate assay was one method chosen to this purpose.[163] This assay is based on the redox properties of LPO, and it measures absorbance of ferric thiocyanate. Mihajevic and colleagues have evaluated this method with regard to the specificity of the response and the choice of standard for comparison.[163] They found that hydrogen peroxides that are often used for calibration of analytical methods, such as *tert*-butyl hydroperoxide (TBH), cumene hydroperoxide, and H_2O_2, might lead to the overestimation of LPO due to the differences in response. No differences were found in the response between different LPO standards. They concluded that the ferrous thiocyanate method gave a rapid and complete measurement of peroxides of mono-, di-, and polyunsaturated acids in biological and food samples.

5.1.6. Aims and objectives

The primary aim of this laboratory study was to contribute a novel aspect to the discussion of optimal intravenous lipid administration in paediatric patients. The question about whether to give intravenous lipids separately from the binary solutions or give them in the form of TNA has primarily focused on sterility issues.[119] Other researchers have investigated the use of TNA in infants and children and found that TNA provided a safe, cost effective way of delivering lipids.[119,129]
Various research groups have quantified both in lipid emulsions and in TNA lipid peroxidation. LPO generation was, however, never compared directly by the same analytical method in the same experimental setting.
In direct response to the unexplored territory, this study aimed to directly compare the two approaches to lipid administration in order to inform the discussion about whether to give lipids separately or as TNA in neonates or children.

Secondary aims of this study were related to laboratory method validation and to the application of a peroxide assay to PN solutions for the first time.
This pilot study aimed to validate a rapid and specific method for detecting *in-vitro* formation of LPO in lipid emulsions for PN. Interestingly, this method had previously only been applied to biological and food samples, and had not been applied to PN solutions.[163] Method development and validation have been based on a report by Mihaljevic and colleagues.[163]

This assay measures LPO after extraction into chloroform; therefore it is specific for lipid hydrogen peroxides. The standard used for comparison is the peroxide of linoleic acid, 13-(S)-HpODE (9,11- Octadecadienoic acid, 13- hydroperoxy [S-(E,Z)]) (Figure 5.4).

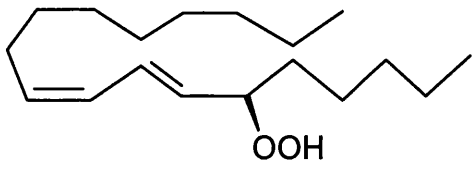

Figure 5.4: Chemical structure of linoleic acid peroxide (13-(S)-HpODE)

After successful validation, the aim was to compare two commercially available lipid emulsions, currently in use for paediatric patients. These lipid emulsions were chosen, as the sponsor was able to provide the emulsions free of charge and the sponsor had previously undertaken work comparing these two emulsions.

Ivelip is made from soybean oil and contains 17% saturated fatty acids, 23% monounsaturated fatty acids, and 60% polyunsaturated fatty acids. ClinOleic is made from 80% olive oil and 20% soybean oil and contains 15% saturated fatty acids, 65% monounsaturated fatty acids, and 20% polyunsaturated fatty acids. Ivelip contains 11 mg α-tocopherol per litre; ClinOleic contains 30 mg α-tocopherol per litre (details extracted from manufacturer's product information).

Two chemical properties of lipid emulsions are important when considering their susceptibility to peroxidation: α-tocopherol content and concentrations of polyunsaturated fatty acids. By breaking the reaction chain, α-tocopherol reduces generation LPO.[154] Polyunsaturated fatty acids are the most likely source for peroxidation.[167] A high concentration of polyunsaturated fatty acids therefore potentially increases susceptibility for peroxidation.

Due to the differences in concentrations of polyunsaturated fatty acids (mainly as linoleic acid) and the differences in α-tocopherol concentrations, it was hypothesised that ClinOleic would generate fewer LPO than Ivelip.

The aim was also to apply this assay to clinically relevant PN solutions. This included measurement of LPO in lipid emulsions and TNA, assessment of the influence of administration procedures on the formation of LPO, and comparison of various environmental factors. Environmental factors of interest were also identified in the literature, and included type of container,[160] storage time,[160] light[126] and oxygen[160] exposure.

5.2. Materials and equipment

Materials and equipment used for this study are listed below.

5.2.1. Parenteral nutrition components

Baxter Healthcare, Compton, UK:

	Batch Number	Expiry
ClinOleic 20%, 100 mL	0201138	03/04
Ivelip 20%, 100 mL	0201137	03/04
Glucose 20% 500 mL	02J31BR	09/04
Primene 10% 100 mL	0201266	09/04
Primene 10% 250 mL	0201251	09/04
Sterile Water 1000 mL	02407B27	05/06

Fresenius Kabi, Runcorn, UK:

	Batch Number	Expiry
Peditrace 10 mL	021V23	09/05
Vitlipid N Infant	1006990AZ	04/04
Solivito N Lyophilisate	JE0908	09/04

5.2.2. Compounding equipment

Baxter Healthcare, Compton, UK:

	Batch Number	Expiry
3-lead transfer set for PN	00K25030687	11/05

Beckton Dickinson, Oxford, UK:

	Batch Number	Expiry
Microlance 3 Needles	7602C03	03/07

5.2.3. Consumables

Beckton Dickinson, Oxford, UK:

	Batch Number	Expiry
Plastipak, Syringes 50 mL	7602C03	03/07

BBraun Carex, Mirandola, Italy:

	Batch Number	Expiry
Evarex EVA (ethyl-vinly-acetate) bags 500 mL	021460	10/07
Evarex barrier (layers of EVA and ethyl-vinly-alcohol) bags 500 mL	021661	12/07

BBraun, Melsungen, Germany:

	Batch Number	Expiry
Discofix, 3-way tap	02K099204	10/05

Baxter Healthcare, Compton, UK:

	Batch Number	Expiry
Administration sets RMC9608	02K18V54DG	10/05

Fisher, Loughborough, UK:

Eppendorf vials 1.5 mL
1 mL pipette tips, certified
200 µL pipette tips, certified

Anachem, UK:

Gilson certified pipettes 20, 100, 200, 1000 µL
(Calibration certificates are enclosed in Appendix 10)

Elkay, UK:

Eppendorf vials 2 mL

5.2.4. Chemicals

Cayman Chemicals, USA:

	Batch Number
13(S)-HpODE 100 µg	188674
Polyphosphoric acid	18520a
4.5 mM ferrous sulphate in 0.2 M hydrochloric acid	18518a
3% ammonium thiocyanate in methanol	18519a
Triphenylphosphine	14644a

Fisher Chemicals, Loughborough, UK:

	Batch Number
Chloroform, analytical grade	0253404
Methanol, HPLC grade	0270438

5.2.5. Equipment

Biomat AC class 2 sseptic cabinet, MAT, Manchester, UK
(Validation certificate is enclosed in Appendix 9)
Astec Sensair Fume Hood, Astec Microflow, Andover, UK
Laboratory fridge, LEC, UK
Vip series –86 Celcius Freezer, Sanyo Scientific, USA
Juan BR 41 Centrifuge
Vortex Mixer, Fisher, Loughborough, UK
SS 40-D Shaking bath, Grant, Cambridge, UK
Dynatec MR 500 Plate reader, Filter 490 nm, Dynatec, USA
BioLink 2.10 Plate reader software, Datatech Laboratories, Virginia, USA
Colleague Infusion pumps, Baxter Healthcare, Compton, UK
96-well plate, Zeiss, Jena, Germany
BOC Gases Nitrogen (Oxygen free), EEC 2317839

5.3. Lipid peroxide assay

5.3.1. Synopsis

Lipid peroxides were quantified by redox reaction with ferrous ions. The resulting ferric ions were detected using thiocyanate ion as the chromogen:

$$ROOH + Fe^{2+} \rightarrow RO^{\cdot} + Fe^{3+}$$
$$RO^{\cdot} + Fe^{2+} + H^{+} \rightarrow ROH + Fe^{3+}$$
$$Fe^{3+} + 5SCN^{-} \rightarrow Fe(SCN)_5^{2-}$$

Ferric thiocyanate absorbs light at a wavelength of 490 nm and colour development was photometrically measured at this wavelength. Interferences from hydrogen peroxides were circumvented by performing the assay after extraction of lipids into chloroform. This assay is available from Cayman Chemicals as a kit for measurement of lipid peroxidation containing 13-(S)-HpODE, polyphosphoric acid, 4.5 mM ferrous sulphate in 0.2 M hydrochloric acid, 3% ammonium thiocyanate in methanol, and TPP.

5.3.2. Preparation

Solvents used were deoxygenated by bubbling with nitrogen for 30 minutes immediately prior to use. The analytical standard, 13-HpODE, was commercially available as a solution of 100 µg in approximately 100 µL ethanol. In order to obtain the appropriate concentration of standard, this solution was diluted by first removing the carrier solvent under a stream of nitrogen and then adding exactly 6.0 mL of ethanol. This diluted standard was stored at -80° Celsius. Samples were diluted with sterile water to a final lipid concentration of 2 mg/mL, *i.e.* lipid 20% solutions were diluted 1:10 and TNA solutions were diluted 1:100. Explorative experiments had shown that higher concentrations of lipids adversely affected the repeatability of the analytical response.

5.3.3. Extraction process

To begin, 500 µL of appropriately diluted sample were transferred into 2 mL plastic vials in triplicate. Next, 500 µL of a 6.7% solution of polyphosphoric acid in methanol were added. To this, 1 mL of cold chloroform was added. After thorough mixing by vortex, the mixture was centrifuged at 0° Celsius for 5 min at 4000 rpm.

The upper aqueous and protein layers were removed and discarded from the vial, and approximately 800 µL of the bottom chloroform layer was transferred into a fresh 1.5 mL vial. Exactly 500 µL of this extract was transferred into a fresh vial. To this, 450 µL of a 2:1 chloroform – methanol mixture was added. Finally, 50 µL of chromogen was added to give a final volume of 1 mL in each vial.

5.3.4. Sample measurement

After leaving the samples for a minimum of 5 minutes (and no longer than 30 min) at room temperature, 300 µL of each sample was transferred onto a 96-well glass plate. Each sample reading was accompanied by a standard reading to take into account potential fluctuations in colour development due to temperature or residual oxygen content of solvents. Absorbance of samples and standards were read at 490 nm using the plate reader.

5.4. Results - Method validation

Method validation was achieved by measuring the following parameters:

a. Linearity of standard response
b. Repeatability of sample measurements
c. Specificity and accuracy
d. Recovery of added standard
e. Linearity of standard addition
f. Effect of matrices on response

5.4.1. Linearity of standard response

The standard response was evaluated by measuring 13-HpODE in eight different concentrations including a blank. Concentrations were 0, 0.5, 1, 1.5, 2, 3, 4, and 5 nmol/mL. These measurements were preformed by adding chloroform/methanol mixture to 0, 10, 20, 30, 40, 60, 80, and 100 µL of 13-HpODE. Final volume in each vial was 1 mL. Figure 5.5 shows that the standard response was linear (R^2=0.996; y=0.0338 x + 0.140) over a range of 0-5 nmol/mL. The correlation coefficient of the least square regression line was 0.996, indicating significant dependence of absorption

of 13-HpODE. Absorbance of the blank is above zero due to the intrinsic red colour of the chromogen.

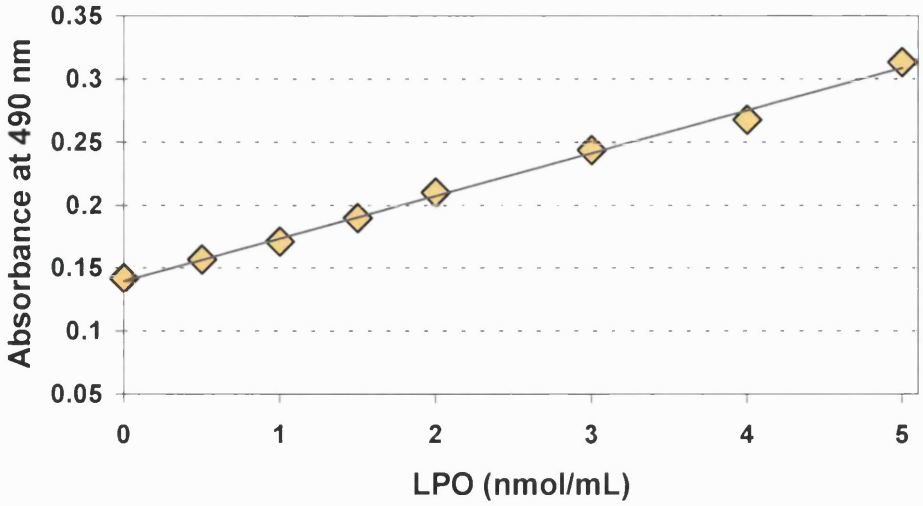

Figure 5.5: Linearity of 13-HpODE standard response

5.4.2. Repeatability of sample measurements

In order to assess repeatability, each sample was measured ten times. Repeatability was to be considered satisfactory, if the coefficient of variance (CV) was below 10%. Table 5.1 summarises the results and shows that repeatability was satisfactory for each sample. The following samples were tested:

Sample A: ClinOleic 20%
Sample B: Ivelip 20%
Sample C: ClinOleic in TNA 2% (without micronutrients)
Sample D: Ivelip in TNA 2% (without micronutrients)
Sample E: ClinOleic in TNA 2% (with micronutrients)
Sample F: Ivelip in TNA 2% (with micronutrients)

TNA contained water, glucose, and amino acids (see Table 5.4 for details). Sodium, potassium, calcium, magnesium, and phosphate were not added to any of the samples.

	Mean absorbance	Standard deviation	CV (%)
Sample A	0.168	0.012	7.5
Sample B	0.177	0.013	7.2
Sample C	0.178	0.011	8.0
Sample D	0.172	0.014	7.0
Sample E	0.179	0.007	4.4
Sample F	0.177	0.010	5.9

Table 5.1: Sample repeatability for samples A-F

5.4.3. Specificity

It was important to ensure that absorbance was due to peroxides and not due to interferences. This aspect was validated using triphenylphosphine (TPP), a potent reducing agent. TPP quantitatively eliminate all peroxides from the sample.[158,168] Any remaining sample absorbance can then be attributed to interferences. If no remaining sample absorbance is measured, interferences can be ruled out.

One of two lipid emulsion samples was treated by adding 10 µL of a 10 mM solution of TPP; the second sample was not treated. If the treated sample had shown a reading close to the blank, interferences could have been ruled out. In order to further validate the use of TPP, another sample was spiked with 2 nmol/mL of 13-HpODE. TPP could be considered a useful tool, if added peroxides were quantitatively reduced.

The following measurement were performed in triplicate:

a. Sample A
b. Sample A + TPP
c. Sample A + 2 nmol 13-HpODE
d. Sample A + 2 nmol 13-HpODE + TPP

Table 5.2 shows that samples treated with TPP had a reduced absorbance below or on the limit of detection (limit of detection was specified in the technical information of the assay kit as 0.025 nmol/mL).

	Absorbance	CV (%)	nmol/mL LPO
Blank	0.284	4.5	-
Sample A	0.306	3.1	0.61
Sample A + TPP	0.285	6.4	0.04
Sample A + 2 nmol 13-HpODE	0.343	2.2	1.61
Sample A + 2 nmol 13-HpODE + TPP	0.293	7.0	0.26

Table 5.2: Absorbance of samples with and without treatment with triphenylphosphine

These results show that measurements obtained with this assay are due to peroxides and not interferences.

5.4.4. Recovery of added standard

Using the data described in section 5.4.3, it was also possible to calculate the completeness of recovery of 13-HpODE during the extraction process.
Because half of extracted volume was used for measurement, it was expected that if 1 nmol of the added 2 nmol of 13-HpODE were measured, then this measurement would signify that recovery was 100%.
Sample A contained 0.61 nmol/mL of LPO. The actual recovery of LPO from 13-HpODE was 1.61 nmol/mL. Of those, 0.61 were from the Sample A, and 1.0 was from 13-HpODE, which successfully indicated that recovery was 100%.

5.4.5. Linearity of standard addition

Recovery of 13-HpODE was previously established for one concentration (section 5.4.4). It was also important to ensure that peroxides were recovered equally if present in differing concentrations. This was achieved by adding varying amounts of 13-HpODE to three different lipid emulsion samples (A, C, and E). As previously described above, half of the extracted solutions were used for measurement; concentrations were therefore doubled for the purpose of this analysis. Linearity of response is shown in Figure 5.6.

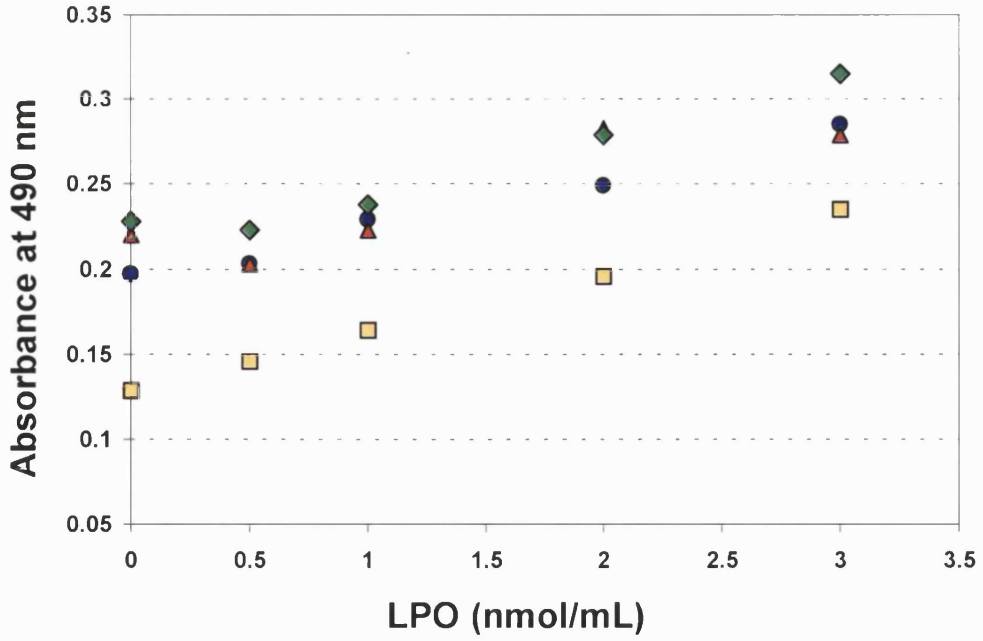

Figure 5.6: Standard response of 13-HpODE without extraction process (yellow) and recovery of 13-HpODE added to samples A (blue), C (red), and E (green)

Linearity of recovered standard (least square regression) as shown in Figure 5.6 was: 13-HpODE (yellow square): y=0.035 x + 0.129; Sample A (blue circle): y=0.030 x + 0.194; Sample C (red triangle): y=0.027 x + 0.206; Sample E (green diamond): y=0.032 x + 0.215. Recover of added 13-HpODE was considered satisfactory for each TNA matrix.

5.4.6. Effect of matrix on response

In order to validate the use of the assay for TNA samples (with a complex matrix), different concentrations of the matrix were prepared (Table 5.1). Different amounts of 13-HpODE were then added to the three matrix concentrations.

50% Matrix		100% Matrix		150% Matrix	
Primene 10%	12.5 mL	Primene 10%	25 mL	Primene 10%	37.5 mL
Glucose 20%	30 mL	Glucose 20%	60 mL	Glucose 50%	36 mL
Lipid 20%	5 mL	Lipid 20%	10 mL	Lipid 20%	15 mL
Water	52.5 mL	Water	5 mL	Water	11.5 mL

Table 5.3: Composition of matrices for matrix validation

Results are shown in Figure 5.7. The response to the three different matrix concentrations varied by less than 5% across a matrix concentration of 50-150%. It can therefore be concluded that the effect of the matrix on response was negligible.

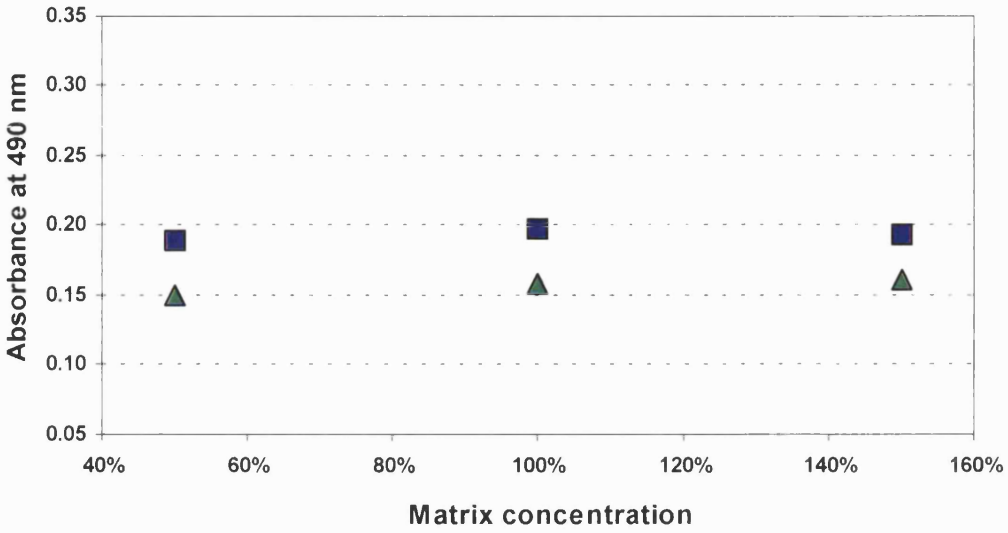

Figure 5.7: Analytical response depending on concentration of nutrients in matrix (100% represents typical neonatal formula) (Addition of 0.5 nmol 13-HpODE (green triangle); addition of 1.5 nmol 13-HpODE (blue square))

After consideration of all validation procedures, this method was considered fully validated for measurement of lipid peroxides in PN solutions and lipid emulsions for PN.

5.5. Experimental

Lipid peroxides were to be quantified in six different samples:

A. ClinOleic 20%

B. Ivelip 20%

C. ClinOleic in TNA 2% (without micronutrients)

D. Ivelip in TNA 2% (without micronutrients)

E. ClinOleic in TNA 2% (with micronutrients)

F. Ivelip in TNA 2% (with micronutrients)

5.5.1. Peroxides in parenteral nutrition

Lipid peroxides were quantified in 20% lipid emulsions (samples A and B) and in TNA (samples E-F) as supplied by the manufacturer. The composition of samples C-F is shown in Table 5.4. TNA and lipid syringes were prepared in a Biomat Class A aseptic cabinet.

In 500 mL	Sample C	Sample D	Sample E	Sample F
Glucose 20%	300	300	300	300
Primene 10%	125	125	125	125
Water	25	25	20	20
ClinOleic 20%	50	-	45	-
Ivelip 20%	-	50	-	45
Peditrace	-	-	5	5
Vitalipid in Soluvito	-	-	5	5

Table 5.4: Composition of PN solutions for lipid peroxide quantification

Samples A and B were stored in 60 mL polypropylene syringes; TNA were stored either in EVA or in oxygen barrier bags. The layers of oxygen barrier bags typically consist of EVA and ethyl-vinyl-alcohol (EVA/Ethyl-vinyl-alcohol/EVA).

Lipid syringes and TNA bags were stored at 25° Celsius for 48 hours (storage details shown below). Samples were measured for peroxides at 0, 6, 12, 24, and 48 hours. Syringes were also stored at 8° Celsius for six days, followed by 48 hours at 25° Celsius. This experiment was performed, as it is common practice in hospitals to store lipid emulsion syringes for several days.[169]

Samples were measured at four and six days; after removal from refrigeration after six days, samples were measured and at 0, 6, 12, 24, and 48 hours. Half of the TNA samples were wrapped in foil for light protection, and all samples were measured in duplicate (light exposure details shown below).

Details of sampling procedures are shown in Table 5.5 – Table 5.7 (each cross represents one measurement).

		Sample A		Sample B	
Sampling time	***Temp***	***48 hrs***	***6 days***	***48 hrs***	***6 days***
0 hrs		xx	xx	xx	xx
6 hrs	25 °C	xx		xx	
12 hrs	25 °C	xx		xx	
24 hrs	25 °C	xx		xx	
48 hrs	25 °C	xx		xx	
4 days	8 °C		xx		xx
6 days	8 °C		xx		xx
+6 hrs	25°C		xx		xx
+12 hrs	25°C		xx		xx
+24 hrs	25°C		xx		xx
+48 hrs	25°C		xx		xx

Table 5.5: Sampling schedule for lipid emulsion in syringes

		Sample C				Sample F			
Sampling time	***Temp***	C	C*	[C]	[C*]	F	F*	[F]	[F*]
0 hrs		xx	xx	xx	xx	xx	xx	xx	xx
6 hrs	25 °C	xx	xx	xx	xx	xx	xx	xx	xx
12 hrs	25 °C	xx	xx	xx	xx	xx	xx	xx	xx
24 hrs	25 °C	xx	xx	xx	xx	xx	xx	xx	xx
48 hrs	25 °C	xx	xx	xx	xx	xx	xx	xx	xx

Table 5.6: Sampling schedule for TNA with ClinOleic; []=Oxygen-barrier; *=light protection

		Sample D				Sample E			
Sampling time	***Temp***	D	D*	[D]	[D*]	E	E*	[E]	[E*]
0 hrs		xx	xx	xx	xx	xx	xx	xx	xx
6 hrs	25 °C	xx	xx	xx	xx	xx	xx	xx	xx
12 hrs	25 °C	xx	xx	xx	xx	xx	xx	xx	xx
24 hrs	25 °C	xx	xx	xx	xx	xx	xx	xx	xx
48 hrs	25 °C	xx	xx	xx	xx	xx	xx	xx	xx

Table 5.7: Sampling schedule for TNA with Ivelip; []=Oxygen-barrier; *=light protection

In order to achieve a constant temperature of 25° Celsius and exposure to light, all TNA bags and syringes were positioned in a water bath near a large southeast-facing window. Containers were floated on the water to allow for adequate light exposure and oxygen

permeation. Inserting an electronic thermometer into a PN bag and into a 60 mL syringe validated the effectiveness of the water bath in providing the appropriate temperature. The water bath was set at a temperature of 25° Celsius. Maximum temperature was reached after 30 minutes in the syringe and after 45 minutes in the PN bag as shown in Table 5.8.

Time (min)	Temperature (° Celsius)	
	PN bag	Syringe
0	17.8	18.2
15	23.8	24.6
30	24.3	25
45	24.5	25
60	24.5	25

Table 5.8: Temperature validation of water bath

The refrigeration unit holding the samples was regularly monitored in order to ensure that the syringes were maintained at 8° Celsius. Lowest temperature measured was 5.8; highest temperature measured was 8.1° Celsius.

5.5.2. Peroxide generation in lipid emulsions and TNA during simulated administration

In order to estimate total peroxide exposure of patients receiving parenteral lipid therapy, generation of peroxides during the administration process was assessed. Samples were prepared in duplicate in oxygen barrier bags. For this experiment, the same containers were chosen for all samples in order to eliminate the effect of the container on the generation of peroxides.

Samples A-F were prepared in duplicate in oxygen barrier bags. Administration sets and infusion pumps were then fitted to each container. The tubing was placed into the 25° Celsius water bath. Another PN bag was fitted to the opposing end of each administration set to capture the sample. Samples were taken from the beginning and the end of the administration set. Pumps were set at 0.4 mL/hour for lipid emulsions and 6.3 mL/hour for TNA (simulating an infusion of 15 mL/day of 20% lipid emulsion and 150 mL/day of TNA).

LPO generation during administration was measured during the course of 48 hours for the lipid emulsions. TNA administration was simulated for a shorter duration of six hours, because the infusion rate of 6.4 mL/hour meant that the emulsion would pass through the administration set in less than four hours. LPO generation was assumed to remain constant after six hours.

To enable sampling without disrupting the simulated administration, 3-way taps were fitted to both ends of the administration set. Aseptic compounding and sampling took place in a Biomat Class 2 aseptic cabinet. Sampling details are shown in Table 5.9 and Table 5.10.

			Sample	
Sampling time	***Rate***	***Temp***	**A**	**B**
0 hrs	0.6 mL/hr		xx	xx
6 hrs	0.6 mL/hr	25 °C	xx	xx
12 hrs	0.6 mL/hr	25 °C	xx	xx
24 hrs	0.6 mL/hr	25 °C	xx	xx
48 hrs	0.6 mL/hr	25 °C	xx	xx

Table 5.9: Sampling schedule for lipid emulsion administration

			Sample			
Sampling time	***Rate***	***Temp***	**C**	**D**	**E**	**F**
0 hrs	6.3 mL/hr		xx	xx	xx	xx
3 hrs	6.3 mL/hr	25 °C	xx	xx	xx	xx
6 hrs	6.3 mL/hr	25 °C	xx	xx	xx	xx

Table 5.10: Sampling schedule for TNA administration

5.5.3. Data analysis

Data were analysed using SPSS 10.0 for Windows. This software was chosen, as it was a familiar tool and allowed the generation of complex figures.

In the following series of figures, bars represent the mean of two sample means; error bars represent +/- 1 standard error of the mean. Samples were prepared in duplicate, and measurements were performed in triplicate. Reference lines in graphs that relate to results for lipid emulsions 20% represent the limit of peroxides in lipid emulsions for intravenous use as defined in the European Pharmacopoeia (*i.e.* 1000 μM).[74] Reference lines in graphs that relate to results for TNA represent the limit for peroxides in the 1:10 dilution (*i.e.* 100 μM).

5.6. Results – Sample measurements

5.6.1. Lipid hydrogen peroxides in lipid emulsions stored in syringes

Lipid emulsions stored at 25° Celsius in polypropylene syringes for 48 hours were tested for peroxide. Figure 5.8 shows that only minimal amounts of LPO were formed. No difference between the two types of emulsions was detected. All measurements were well below the European Pharmacopoeia limit.

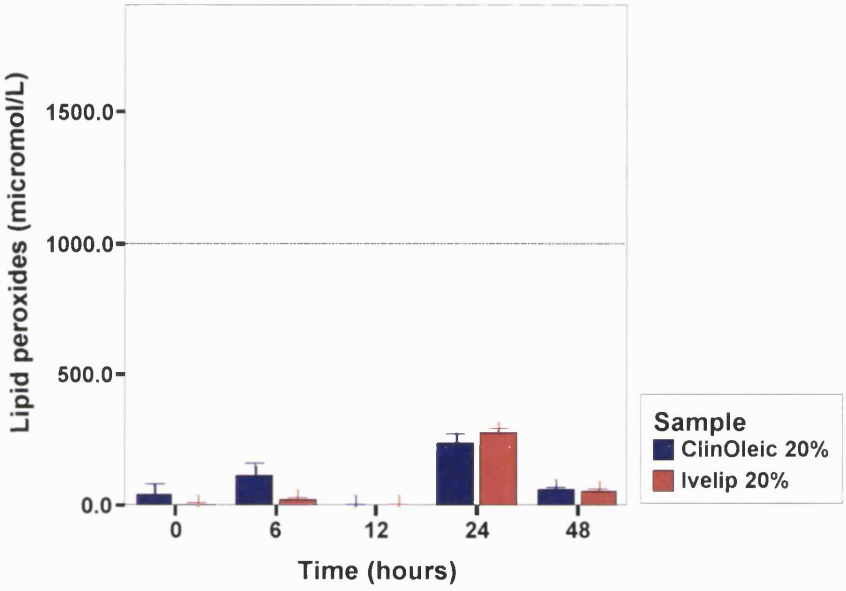

Figure 5.8: LPO concentrations in 20% lipid emulsions stored at 25° Celsius for 48 hours in syringes

Additionally, syringes were stored for six days at 8° Celsius, followed by 48 hours at 25° Celsius. Figure 5.9 shows that LPO increased during the four days of storage. After transfer from the refrigerator unit to 25° Celsius, LPO increased to over 1.7 mM/L.

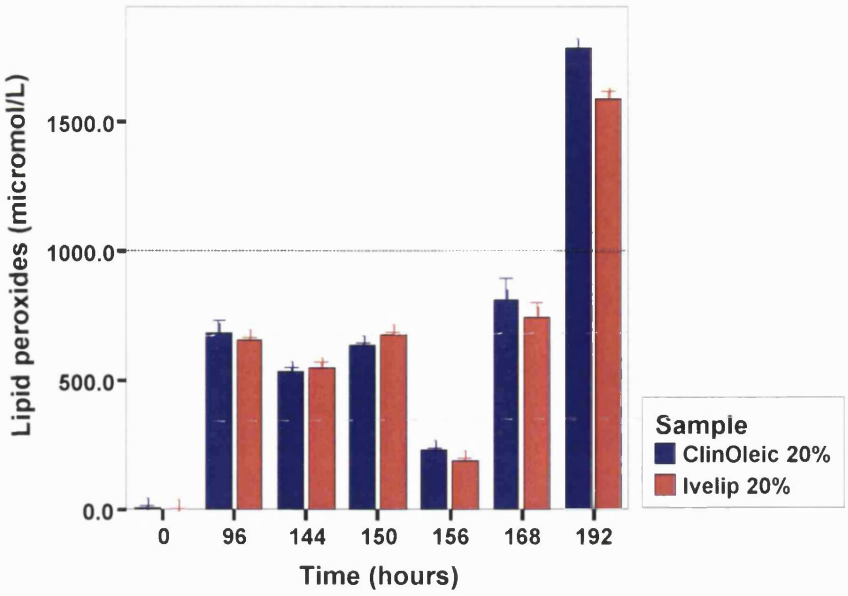

Figure 5.9: LPO concentrations in 20% lipid emulsion stored at 25° Celsius for 6 days in syringes

5.6.2. Lipid hydrogen peroxides in total nutrient admixtures

Four different types of TNA were tested for levels of LPO. These admixtures were then stored under four different conditions with regard to oxygen and light exposure. Figure 5.10 shows that LPO were generated in TNA containing ClinOleic immediately after compounding. Notably, concentrations of LPO did not increase with time. Storage conditions did not have a significant effect on the LPO concentrations.

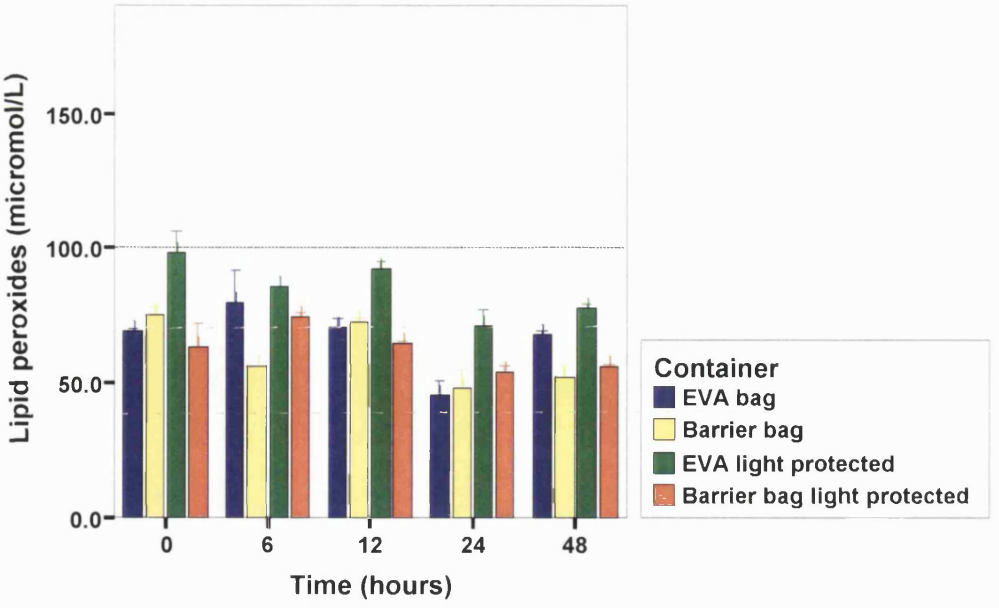

Figure 5.10: LPO concentration in TNA (Sample C - ClinOleic) stored at 25° Celsius for 48 hours

TNA containing Ivelip showed no measurable LPO formation for the first six hours after compounding, as shown in Figure 5.11. After 12 hours, LPO increased to 50 μM/L.

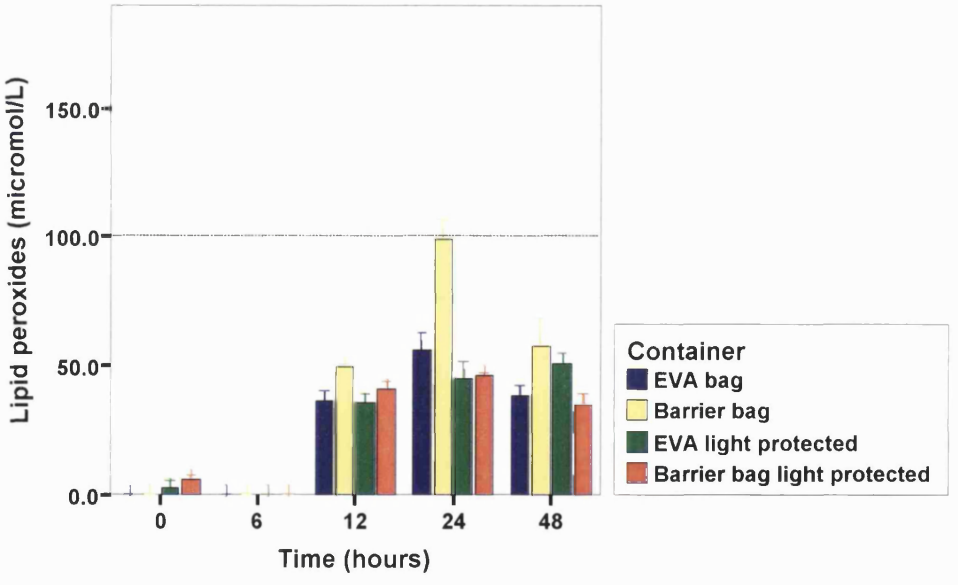

Figure 5.11: LPO concentration in TNA (Sample D - Ivelip) stored at 25° Celsius for 48 hours

The effect of micronutrients on LPO formation was investigated. Vitamins and trace elements were added to TNA containing either ClinOleic or Ivelip. Figure 5.12 and Figure 5.13 show the amounts of LPO formed in TNA containing micronutrients. Light and oxygen protection did not affect LPO levels. After six hours, TNA containing ClinOleic showed higher levels of LPO compared to TNA containing Ivelip.

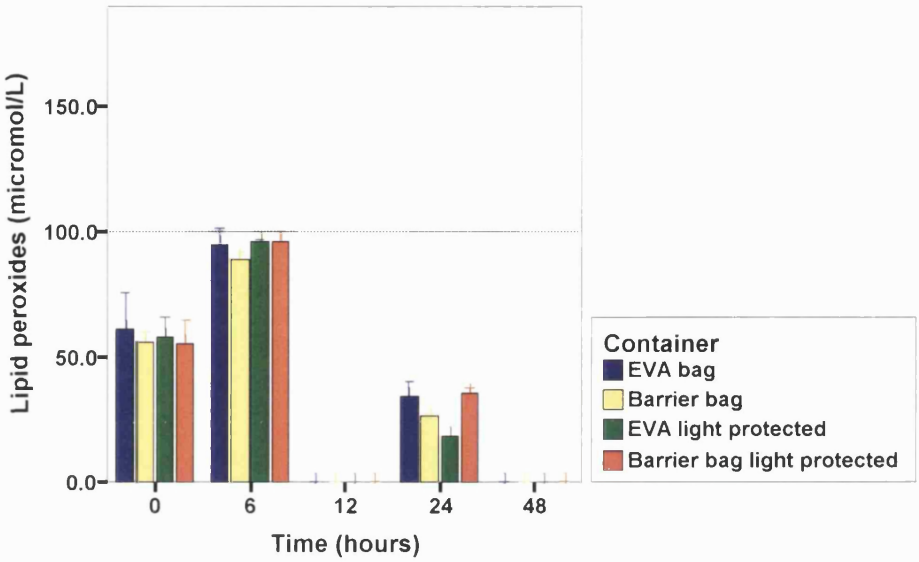

Figure 5.12: LPO concentration in TNA (Sample E – ClinOleic + Micronutrients) stored at 25° Celsius for 48 hours

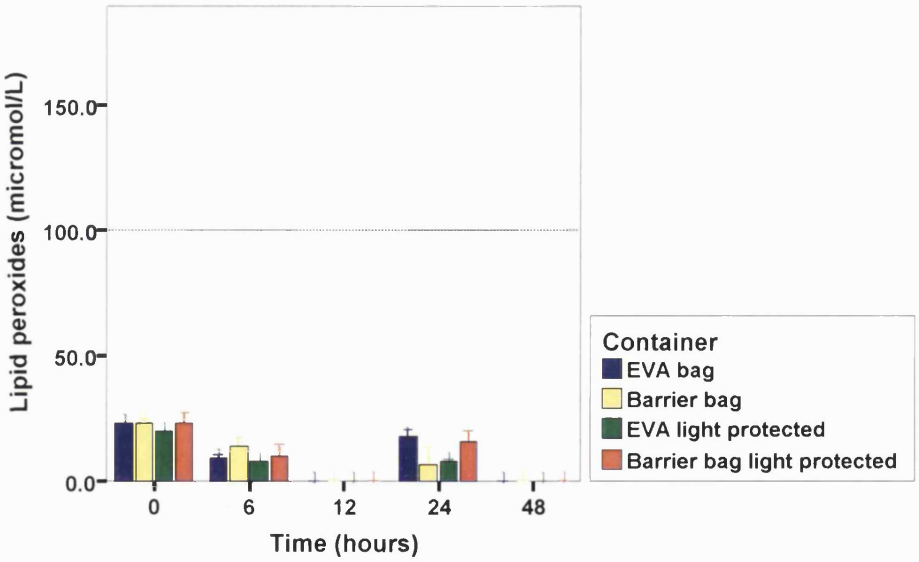

Figure 5.13: LPO concentration in TNA (Sample F – Ivelip + Micronutrients) stored at 25° Celsius for 48 hours

5.6.3. Peroxide generation during administration

In order to estimate the total amount of LPO administered to patients, peroxide formation was investigated during the administration process. Table 5.11 summarises the additional amount of LPO formed during administration in 20% lipid emulsions.

µmol/L	0 hrs	6 hrs	12 hrs	24 hrs	48 hrs
Sample A	0.0 ± 0.0	54.6 ± 54.6	43.8 ± 43.7	137.5 ± 50.0	5.9 ± 5.9
Sample B	0.0 ± 0.0	91.0 ± 18.2	75.0 ± 50.0	81.3 ± 18.8	147.0 ± 5.9

Table 5.11: LPO generation during simulated administration of 20% lipid emulsions

In the TNA samples, additional LPO generated during administration was also measured. Results are shown in Table 5.12.

µmol/L	0 hrs	3 hrs	6 hrs
Sample C	4.7 ± 3.6	0.0 ± 0.0	1.7 ± 0.6
Sample D	3.5 ± 1.2	12.0 ± 5.2	7.5 ± 1.7
Sample E	3.0 ± 1.8	2.9 ± 1.8	5.2 ± 1.8
Sample F	0.6 ± 0.6	7.5 ± 0.6	2.3 ± 2.3

Table 5.12: LPO generation during simulated administration of TNA

5.6.4. Estimated intake of lipid peroxides during parenteral nutrition

LPO concentrations measured in this study facilitate an estimation of daily LPO intake from PN in neonates.

The assumption was made that lipid intake for a typical neonate is 3 g/kg/day (*i.e.* 150 mL of TNA and 15 mL of lipid emulsion 20%). Light protection or oxygen barrier bags were not taken into consideration (*i.e.* calculations were based on the means), because their effect on LPO concentrations was negligible.

Cumulative LPO intake over 48 hours was calculated using the results shown in sections 5.6.1-5.6.3 (Table 5.13).

	6 hrs	12 hrs	24 hrs	48 hrs
			µmol/kg	
ClinOleic 20%	0.16	0.79	1.12	6.80
ClinOleic 20% (after 6 days storage)	1.99	4.58	6.66	20.92
Ivelip 20%	0.00	0.43	0.99	6.36
Ivelip 20% (after 6 days storage)	2.06	4.93	6.94	19.36
TNA ClinOleic (Sample C)	3.04	5.88	11.64	20.13
TNA Ivelip (Sample D)	0.21	0.50	4.09	14.42
TNA ClinOleic (Sample E)	2.24	5.97	6.36	11.42
TNA Ivelip (Sample F)	0.86	1.32	1.49	3.64

Table 5.13: Estimated cumulative intake of LPO per kg body weight over 48 hours in neonates

Highest exposure to LPO occurred if ClinOleic 20% was stored for six days prior to administration. Exposure was lowest if TNA with Ivelip and micronutrients was administered.

5.7. Discussion

This photometric quantification method for LPO to PN solutions was utilised for the first time in these study experiments for a new application. Various validation steps were performed showing that the method was specific for LPO and that the nutrition matrix did not interfere with the assay response.

The ferric thiocyanate assay was selected for this purpose because it had previously been suggested that this method provided an easy, rapid, and sensitive measurement of LPO in biological samples.[163] A lipid peroxide (*i.e.* 13-(S)-HpODE) was chosen as the standard for comparison, rather than inorganic hydrogen peroxides as used in the FOX and iodine titration method. It has previously been shown that these inorganic peroxides show a lower analytical response than LPO.[163] Previously published results that have used inorganic peroxides for comparison might have overestimated the level of contamination in PN solutions.[165]

This method also proved to be a rapid method for quantifying LPO in PN solutions; extraction and measurement of eight samples in triplicate took less than two hours. The amount of solvents used was 1 mL of chloroform and 0.5 mL of methanol for each sample extraction. This can be compared to 50 mL of solvent required for iodometric titration.[65] A majority of the chemicals and equipments used would be standard in most laboratories. This method might potentially be a useful tool for measurement of LPO in hospital pharmacies as part of routine quality control monitoring. The only equipment that might not be standard in every laboratory was the –80° C freezer; this freezer was required for storage of the linoleic acid peroxide standard.

Although this method allowed measurements of as little as 0.5 nmol LPO in 1 mL of extracted samples, the sensitivity was reduced due to the fact that samples had to be diluted prior to the extraction of LPO. Lipid emulsions were diluted 1:100 and TNA was diluted 1:10. This was necessary to achieve good reproducibility, but meant that sensitivity was reduced to 50 μM in 20% lipid emulsions and 5 μM in TNA. As values reported in the literature were found to be much higher than 5 or 50 μM, it was considered that the sensitivity of this method was sufficient to detect changes in LPO concentrations.[160,164] In order to further validate the use of this assay, future work should compare this method to previously validated HPLC methods.[165]

After validating this assay for use in parenteral lipid emulsions, various clinically relevant PN solutions were tested for LPO levels.

Firstly, lipid emulsions were tested as supplied by the manufacturer. These 20% emulsions are usually infused in paediatric patients using syringe drivers, and they are aseptically transferred into syringes prior to administration. The typical duration of infusion is 24 hours, but sometimes syringes are left *in-situ* for 48 hours. In some hospitals, syringes are prepared by hospital pharmacy staff in advance and stored for several days in a refrigerator until use.[88] The experimental design included storage 20% lipid emulsions in syringes at an elevated room temperature of 25° C (as would be expected to be the case on neonatal wards) for 48 hours and storage syringes in a refrigerated environment for 6 days, followed by 48 hours at 25° C.

Results from this experiment showed that LPO formation in syringes stored immediately at 25° C was minimal (Figure 5.8). No differences between ClinOleic and Ivelip were detected. Syringes first stored at 8° C for six days however showed a considerable increase in LPO, especially after 48 hours at 25° C (Figure 5.9). After six days in refrigerated conditions and 48 hours at 25° C, LPO levels exceeded the European Pharmacopoeia maximum recommended levels 1.7 times.[74]

Steger and colleagues stored various 20% lipid emulsions in containers for PN at room temperature for up to 30 days and found that levels of LPO rose to 3 mM (measured by iodometric titration).[160] Although these levels were very high, it must be pointed out that this experimental design was not relevant in clinical practice because lipid emulsions are unlikely to be stored at room temperature for such long periods in actual clinical practice. The increased levels of LPO measured in syringes in this study suggest that syringes might not be an ideal storage medium for lipid emulsions that are not used immediately. Syringes stored at 25° C for 48 hours directly after their preparation did not show an increase in LPO levels. This practice might not contribute significantly to the oxidative load infused in patients receiving PN.

Secondly, TNA solutions were tested for LPO. TNA contained either ClinOleic or Ivelip 2g/100 mL. Results showed that LPO concentrations were lower in TNA containing Ivelip compared with ClinOleic (Figure 5.10-Figure 5.13). As Ivelip contains more unsaturated fatty acids, it had been expected to show higher levels of LPO. A possible explanation for the increased concentration of LPO in ClinOleic could be related to the way in which ClinOleic is manufactured. Unfortunately, this has not been further explored and remains a speculation.

Solutions were tested with and without added micronutrients to determine whether micronutrients affect the amounts of LPO generated. Conflicting reports regarding the

role of micronutrients have been published. Some suggest that multivitamin solutions contribute significantly to the total peroxide load of PN,[126] whereas others suggest adding micronutrients to lipid emulsions for protection from LPO.[66]

TNA were either stored in EVA or oxygen barrier bags to test the influence of oxygen diffusion during storage on peroxidation. Half of the samples were also light protected, in response to reports, which have shown that light protection reduces LPO concentrations.[66,120,126] It was hypothesised that LPO generation would be reduced in oxygen barrier and light protected containers.

Results showed that LPO concentrations were lowest in TNA containing micronutrients and Ivelip, and highest in micronutrient-free TNA containing ClinOleic (Figure 5.10 and Figure 5.13). Highest levels reached were 100 μM. Storage conditions did not appear to affect LPO generation significantly. This was surprising as previous reports had always shown significant differences between light exposed and light protected solutions.[120,126,166] Laborie and colleagues measured up to 300 μM of TBH equivalent (by FOX method) in TNA unprotected from light, compared to 100 μM of TBH equivalent in light protected TNA.[126] They also showed increased levels of urinary peroxides in infants receiving PN that had been exposed to light.[120] In this study, light exposure was not quantified. Containers were placed into a water bath located near a large window. As experiments were carried out during the winter months, light intensity was relatively low. This fact might explain the lack of difference between light protected and not protected solutions.

Compared to EVA bags, oxygen barrier bags had previously been reported to offer protection from LPO generation.[160] It is difficult to compare results from this study with the work undertaken by Steger and colleagues because their experimental design was very different. They investigated LPO generation in 20% lipid emulsion stored in containers for TNA for up to a month. Differences in LPO between different containers only became apparent after several days. This study measured LPO in TNA in regular intervals during 48 hours. The time period might have been too short to detect differences. It is also possible that the amount of oxygen already present in the solution due to the compounding process was of such concentration that the protection from further oxygen diffusion through the container wall was insignificant.

Silvers and colleagues investigated the role of light exposure of PN in the administration set on total peroxides generated during the infusion process, and then found that this significantly contributed to the LPO concentration administered to

patients.[66] It was therefore considered important not only to measure LPO in containers, but also at the end of a simulated infusion in order to calculate total LPO administered to patients. Infusions were simulated for a neonate weighing 1 kg and receiving 3g of lipids per day, either as 15 mL of 20% lipid emulsion or 150 mL of TNA. Infusion rates were therefore calculated to be 0.6 mL/hour for 20% lipid emulsions and 6.3 mL/hour for TNA.

Results showed that some LPO were generated during the infusion process (Table 5.11 and Table 5.12). More LPO per litre of emulsion were found in 20% lipid emulsions, but this can be attributed to the ten times higher concentration of lipids in those emulsions.
Additional LPO generated during the simulated infusion process can be considered insignificant, when compared to LPO concentrations generated in the container during storage.

Throughout this study, no differences in LPO generation were detected between ClinOleic and Ivelip. This was significant because, as previously mentioned, differences would have been expected due to the different concentrations of unsaturated fatty acids and α-tocopherol in each of these two lipid emulsions.
The absence of differences detected *in-vitro* does not mean that amounts of polyunsaturated fatty acids and α-tocopherol do not influence oxidative stress caused by lipid infusion *in-vivo*. Antebi and colleagues performed a study comparing ClinOleic to soybean-based emulsion.[170] They measured concentrations of thiobarbituric-acid-reactive substance in lipid emulsions incubated with phenylhydrazine. They found that ClinOleic was more resistant to oxidation. This might indicate that, although this study of LPO in lipid emulsions did not show a decreased level of peroxides, the level of *in-vivo* resistance to a hyperoxic environment might be higher with ClinOleic.

A surprising outcome of the application of the ferrous thiocyanate method was that results were relatively variable with time. It had been expected that LPO levels would be lowest at time zero, and then either increase with time or remain constant, as is the case in some published reports.[160] However, on several occasions, LPO levels dropped after 12 hours or 24 hours. A similar observation was reported by Laborie and colleagues; in the presence of lipids, total peroxides were lower after six hours than after one hour.[126] These investigators did not interpret this occurrence. It can be

hypothesised that LPO react further to form a non-oxidising product, and this would account for the reduction in detectable LPO. This observation requires further investigation.

Using all the results generated, it was possible to calculate an example of total LPO exposure for a neonate receiving lipid infusions over 48 hours.
Additionally, this calculation exercise enabled the investigation of the primary aim of the study; the LPO concentrations administered in separate lipid infusion and TNA were directly compared.
This calculation showed that a neonate would be exposed to 3.6 to 20.9 μM LPO over 48 hours. Highest intakes occurred with 20% lipid emulsions, which had been stored for 6 days before administration. TNA with ClinOleic revealed similar amounts of LPO. Lowest intake occurred with fresh 20% lipid emulsion and with TNA containing micronutrients and Ivelip.
Currently, it is not known if these levels of LPO pose a clinically relevant risk to patients. It is also not known how clinically relevant Pharmacopoeia limits of LPO in intravenous lipid emulsions are, especially in premature neonates, whose oxidative defence might be impaired.

The primary research question for this laboratory study was to investigate a new aspect in the discussion about whether or not lipid emulsions should be administered separately or as TNA.
In conclusion, no major differences were found in the amount of LPO potentially administered to patients receiving lipids separately or as TNA. It is crucial that all pharmaceutical and clinical aspects are taken into consideration when discussing the preferred administration route of intravenous lipids.

Further validation work is recommended in order to compare this method with other methods that measure lipid peroxides exclusively, for example HPLC. Total peroxides should also be investigated for comparison. Further application of this method could include measurement of different formulae solutions, which contain electrolytes and minerals, and the comparison of different commercial PN products. The influence of phototherapy on LPO formation also warrants further investigation. Most importantly, toxicological consequences of infusing LPO need to be investigated, especially in

premature neonates who are at risk of having impaired antioxidative defences. This will enable realistic and relevant limits for LPO in PN solutions to be established.

6. Overall discussion and conclusions

The overall objective of this research project was to gain a better understanding of neonatal and paediatric PN in Europe and to contribute to discussions related to the optimisation of care. One focus throughout the project was the use of standard PN. Also, the aim was to focus in more detail on one aspect of administration practice related to the use of intravenous lipid emulsions.

A variety of research methodologies were employed, including qualitative and quantitative methods for questionnaire and interview surveys, non-interventional clinical research, and laboratory-based pharmaceutical and analytical techniques.

6.1. Summary of findings

The practice of neonatal and paediatric PN in Europe was studied for the first time. Prescribers were usually physicians, although in the UK pharmacists also performed prescribing roles. Major differences were found between the countries with regard to the aseptic preparation of PN solutions. In the UK, aseptic compounding units were usually available, but this was not the case in many of the other countries studied. In Italy, compounding of PN commonly took place on the ward, and in Germany, additions were regularly made on the ward.

Aseptic manipulation of PN bags increases the risk of microbial contamination. Therefore this risk should be kept to a minimum, and compounding should take place in controlled aseptic environments. Details about the environment in which manipulations occurred on the wards were not investigated, but it can be assumed that this practice increases the risk of microbial contamination compared to the practice of only permitting manipulations within licensed aseptic facilities in pharmacy departments.

In-line filters have been recommended for PN administration in paediatric PN, and this study found that filters were indeed used frequently. Over one quarter of hospitals did not use administration filters at all; neonates and children in these hospitals were, therefore, at risk of receiving increased amounts of particulate matter from PN.

Light protection has been investigated with regard to vitamin stability and peroxidation, and it was shown to be beneficial to protect both PN container and administration set,

especially if phototherapy light is used.[81,166,171] This study found light protection of containers to be common practice, but the administration set was rarely protected. Investigations of lipid peroxidation found that light protection did not influence peroxide generation. However, hydrogen peroxide generation and vitamin stability were not studied; light protection might be required to protect PN solutions from these instabilities.

Prescribing practice was audited in ten GH and TH in the UK and in six University hospitals in Europe. The most important single factor contributing to differences in prescribed nutrition was the day after first commencement of PN. Body weight only had a small impact on macronutrient prescribing. Concurrent enteral feeding also had little effect on PN prescribing practice. Administration of prescribed PN was satisfactory in most cases, but, in approximately one third of cases, less than 80% of prescribed PN was administered. Reasons for this were not investigated, but it is important to note that this discrepancy might contribute significantly to underfeeding. Generalisability of results is limited, as data were collected from a relatively small number of hospitals.

The survey showed that StSol were used in several hospitals. For neonates, these solutions were typically unlicensed in-house manufactured solutions. The main reasons for the introduction of StSol included resource pressures on pharmacy compounding facilities and desirability of increased quality control with StSol compared to individually compounded bags.
Perceptions of prescribers regarding the composition of an ideal StSol differed greatly. Detailed analysis of prescribing practice revealed that amino acids and glucose concentrations in PN prescribed for neonates increased greatly during the course of PN, especially in TH and ITH. As a result, decisions about the introduction of StSol should take into consideration that concentration requirements differ from patient to patient, especially during the first few days of PN.

Peroxidation of lipid emulsions was studied in more detail as one aspect of PN risk management. A novel assay, which was used for this application for the first time, was successfully validated.
Lipid peroxidation was greatly increased if the emulsions were stored in syringes for more than fours days prior to administration.

6.2. Conclusions

- Compounding practice of parenteral nutrition solutions was diverse throughout Europe and optimal aseptic conditions were not always applied.

- Standardised parenteral nutrition was used in several hospitals in Europe; calculations based on typical fluid intake indicated that these solutions might not provide sufficient nutrients to neonatal patients.

- Prescribed parenteral nutrition was usually administered to neonatal patients in satisfactory amounts, but prescribers should be aware that in some cases insufficient amounts were administered and that constant monitoring of nutritional intake might be required to ensure satisfactory intake.

- Amino acid intake in premature neonates was below current recommendations. This was due to low amounts of amino acids prescribed for parenteral nutrition.

- The ferric thiocyante assay, performed in chloroform, provided a useful tool for quantification of lipid peroxides in emulsions for intravenous feeding.

- Lipid peroxides were generated in large amounts when intravenous lipid emulsions were stored for more than four days.

- Lipid emulsion given separately from the binary solutions potentially increases the amount of lipid peroxides infused when the emulsion is stored for several days in syringes.

- Nutritional care of neonatal and paediatric patients can potentially be optimised by ensuring nutritional adequacy of standardised nutrition, by developing international guidance for aseptic manipulation of containers for parenteral nutrition, and by internal monitoring of nutritional intake in neonates.

6.3. Future work

This project has identified areas for future investigations that were beyond the scope of this work.

With regard to StSol further assessment of nutritional adequacy is recommended. Results from both the survey and neonatal nutrition study indicate that some of the StSol currently in use might not provide adequate nutrition support. It is desirable that future work compares standard versus individual prescribing in terms of clinical and nutritional outcomes.

This project has uncovered that several hospitals use StSol, and the author of this thesis estimates that the number of StSol used will rise in the future due to issues related to good manufacturing practice, clinical governance, and the way in which hospitals obtain manufacturing licences.[88,89] It is important that all healthcare professionals undertaking standardisation are encouraged to ensure that nutritional support is at least equal to that in individualised PN regimes. Pharmacy departments should also investigate how StSol affect their service, both in terms of patient safety and efficacy. The overall changes in pharmaceutical and clinical practice linked to the introduction of StSol should also be investigated with regard to cost effectiveness.

Continuous development of practice guidelines for prescribing, compounding, and administration of PN is a key role for national and international special interest groups. Furthermore, a multi-centre randomised controlled trial should be undertaken comparing StSol to individualised regimens in neonates. Only a rigorous trial of this kind would allow a true comparison of both practices. Such a trial could be performed in a double blind fashion where only the pharmacy department know whether the PN bag is standard or not. Outcome measurements could include total daily energy intake, biochemical imbalances, growth and weight gain, and other clinical indicators, such as occurrence of sepsis, length of hospitalisation, and progression of enteral feeding. Additional measures could include timesaving for the pharmacy department and reduction in prescribing time. Although such a trial is possible, several difficulties with regard to the execution can be envisaged: a multi-centre trial would have to be conducted to have access to sufficient patient numbers, and to make the trial relevant to other hospitals. In order to compare the different centres, their practice (e.g. compounding and prescribing practice) would have to be somewhat standardised. Alternatively, each centre could act as their own comparison. Such a trial would be lenghy and expensive to undertake.

Discrepancies between prescribed and administered PN occurred frequently. Future studies should investigate this area further; a focus on reasons why prescribed PN was not administered. It might then be possible to improve nutrition support by developing strategies that allow more complete administration of PN.

The clinical study gave an overview of practice in general district hospitals (GH) and teaching hospitals (TH) in the UK. General hospitals in other European countries were not included because of the infeasibility of sufficient data collection. Investigating practice in general hospitals across the continent could widen the international scope of this part of the project.

With regard to oxidative stress and PN, more work is required in order to understand the clinical implications of infusing solutions that are contaminated by peroxides. This is the only way it is possible to define relevant limits in PN solutions, particularly for neonates and children. Clinical studies have already been undertaken investigating urinary peroxides after infusion of lipid emulsion.[166] Further studies should focus on the relationship between LPO levels in solutions for infusion, comparing those to urinary or plasma LPO levels. Long-term outcome related to oxidative stress, for example, occurrence of retinopathy of prematurity, should also be studied.

In the meantime, analytical methods must be carefully reviewed for suitability. For further validation purposes, the assay developed for this project should be compared to HPLC methods.

In general, lipids are usually given separately to paediatric patients, and almost always given separately to neonates. It would be desirable if future investigation focused on improved clinical outcomes, such as comparing the amounts of lipids given by TNA or separate infusion.

The electronic data collection tool was successfully utilised during the clinical study. In future, this tool could be developed further to allow automatic assessment of practice, *e.g.* monitoring of prescribing and nutritional intake. During the course of the study it became clear that many prescribers do not have access to such a system that allows them to overview their own PN practice. It would be desirable that prescribers and nutrition support teams are able to review their own practice regularly and in a straightforward way.

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APPENDIX 1:

Questionnaire for exploratory interviews

Pharmacy Practice Research Unit
School of Pharmacy and Pharmacology
University of Bath
Claverton Down
Bath BA2 7AY
England

Bettina Klüttgens

October 2000

European Practice in Paediatric Parenteral Nutrition

Please tick *one box* for each question unless otherwise specified.

Section A: General Information

1. Is your hospital a specialised children's or neonatal hospital?

   a) Children's:

   ❑ Yes ❑ No

   If no, do you have a specialist children's unit?

   ❑ Yes

   ❑ No

   b) Neonatal:

   ❑ Yes ❑ No

   If no, do you have a specialist Neonatal unit?

   ❑ Yes

   ❑ No

2. How many children's/ neonatal beds are there in your hospital?

   Children's .....
   Neonates .....

3. How many paediatric patients (neonates *and* children) are receiving intravenous nutrition in an average week in your hospital?

   ❑ 0-1 ❑ 11-15

   ❑ 2-5 ❑ 16-20

   ❑ 6-10 ❑ >20

4. Please describe your role in the supply of parenteral nutrition.

.....

.....

.....

5. Who is involved for the decision making in parenteral nutrition prescribing?

(Tick as many boxes as necessary)	Please specify their role:
❑ Pharmacist.....	.....
❑ Paediatric surgeon.....	.....
❑ Paediatric gastroenterologist	.....
❑ Neonatalogist.....	.....
❑ General paediatrician.....	.....
❑ Biochemist.....	.....
❑ Dietician.....	.....
❑ Nurse.....	.....
❑ Other (Please specify:.....	.....
.....)	

6. Do you supply parenteral nutrition for paediatric patients at home?

❑ No

❑ Yes

If yes,

a) How many patients receive parenteral nutrition at home in a typical week?
.....

b) What is the approximate percentage of solutions that are supplied as all-in-one?
.....

Section B: Supply of Parenteral Nutrition

7. Is there a unit in your hospital that compounds parenteral nutrition?

❑ Yes ❑ No

8. What guidelines do you use to define nutritional targets of parenteral nutrition?
(Please tick as many boxes as necessary)

❑ In-house policy
❑ Local/Regional recommendations
❑ Computer Program
❑ National recommendations
❑ International recommendations
❑ None
❑ Other

Please specify the one/ones you ticked:

.....

.....

9. Do you use computer programs to support the *prescribing* of parenteral nutrition?

❑ Yes ❑ No

If yes, which one/ones?

.....

.....

10. Do you use computer programs to support the *compounding* of parenteral nutrition?

❑ Yes ❑ No

If yes, which one/ones?

.....

.....

11. What ingredients do you use for the compounding of parenteral nutrition in different age groups? Please specify *which brand* you use in which *age group*.

Fat:.....

.....

Amino acids:.....

.....

Vitamins:.....

.....

Trace elements:.....

.....

12. How do you supply the fat emulsion? *(Tick as many boxes as necessary)*
Please specify *age groups* and *approx. percentages*

- ❑ Separately.....

  .....

- ❑ All-in-one .....

  .....

13. What is your policy about the addition of *vitamins* to parenteral nutrition in different age groups.

a) When do you start including vitamins?

.....

.....

.....

b) How many days per week do you include vitamins in parenteral nutrition?

.....

.....

.....

c) Do you include Vitamin K in parenteral nutrition?

❑ Yes ❑ No

If yes, please specify the use of vitamin K in different age groups (i.e. amount of Vitamin K and number of days per week).

.....

.....

.....

.....

14. What is your policy about the addition of *trace elements* to parenteral nutrition solutions.

a) When do you start including trace elements?

.....

.....

.....

b) Which trace elements do you include? (If you use a commercially available mixture please specify the brand.)

.....

.....

.....

15. a) What shelf life do you *assign* for the nutritional solutions and why?

.....

.....

.....

b) What would be the ideal shelf life for parenteral nutrition solutions?

.....

16. What kinds of end-control do you use for the *compounded individual* bag? *(Tick as many boxes as necessary)*

- ❑ None
- ❑ Visual check
- ❑ Weighing
- ❑ Osmolarity
- ❑ Electrolyte assay
- ❑ Sterility/Pyrogens
- ❑ Other (Please specify:.....)

Section C: Standardisation

17. Do you use *pre-mixed* standard solutions for some patients?

- ❑ Yes –**Please answer question 18 to 25.**
- ❑ No –**Please go to 26 (page 9).**

18. Why did you decide to use one standardised solution for some patients?

.....

.....

.....

19. In which year did you introduce the standard regimen/regimens?

.....

20. How do you produce these standard solutions?

- ❑ Bags are prepared every day
- ❑ Bags are produced in batches of .....bags (Please specify)
- ❑ Other (Please specify:.....)

21. Where does the formulation for standardisation come from?
(Tick as many boxes as necessary)

- ❑ Developed in-house
- ❑ Other Hospital
- ❑ Regional recommendations
- ❑ National recommendations
- ❑ Other (Please specify:.....)

22. Do you have different standard solutions for different age groups?

❑ Yes

If yes, what are these age groups?

.....

.....

.....

❑ No

If no, which age group receives standard nutritional solutions?

.....

.....

.....

23. Do you use commercially available solutions as standard solutions?

❑ Yes

If yes, which one/ones?

.....

.....

❑ No

24. Do you produce the standard TPN solution/solutions in-house?

- ❑ No
- ❑ Yes

If yes, please specify what ingredients the solution/solutions contains and where/when each solution is used.

	Solution 1	Solution 2	Solution 3	Solution 4
Used for:				
Glucose	❑	❑	❑	❑
Electrolytes	❑	❑	❑	❑
Amino acids	❑	❑	❑	❑
Vitamins	❑	❑	❑	❑
Trace elements	❑	❑	❑	❑
Fat	❑	❑	❑	❑
Other (please specify.....)	❑	❑	❑	❑

25. What kinds of end-control do you use for the *compounded standard* solutions? *(Tick as many boxes as necessary)*

- ❑ None
- ❑ Visual check
- ❑ Weighing
- ❑ Osmolarity
- ❑ Electrolyte assay
- ❑ Sterility/Pyrogens

Other (Please specify:.....)

Please go now to the end of the questionnaire.

26. Why do you compound *each* bag individually?

.....

.....

.....

.....

27. Have you taken any steps towards standardising your parenteral nutrition for children and neonates?

❑ Yes ❑ No

(Tick as many boxes as necessary)

❑ Children

❑ Neonates

28. Would you be prepared to use standardised solutions?

❑ Yes ❑ No

If no, why not?

.....

.....

.....

.....

.....

Please include copies of (where applicable):

- ❑ Standard formulas
- ❑ Nutritional targets
- ❑ Compounding protocols
- ❑ Other documents that you might consider to be relevant for this survey

Thank you for taking the time to complete this questionnaire.

I will send you a copy of my results after visiting hospitals in France, Germany, Italy, Spain, and the UK.
If you wish to comment on paediatric parenteral nutrition and the standardisation of nutritional solutions, please use the space on the back of this page.

APPENDIX 2:

Cover letter and questionnaire for postal survey (cover letter in five languages, English version of questionnaire only)

UNIVERSITY OF BATH

Bettina Klüttgens

Department of Pharmacy and Pharmacology
Bath BA2 7AY
England

Phone +44-1225-323107
Fax +44-1225-826114
Mail: prpbuk@bath.ac.uk

Bath, April 2001

Dear ,

I would very much like you and your hospital to participate in a major European survey into the practice of neonatal and paediatric parenteral nutrition.

I am a research Pharmacist at the University of Bath. I work with Graham Sewell, Professor for Pharmacy Practice at the University of Bath, and Tony Nunn, Chief Pharmacist at Alder Hey Children's Hospital Liverpool.

The aim of this survey is to evaluate how paediatric parenteral nutrition is managed in Europe, and if there is a potential for standardisation in different age or weight groups.

By answering the attached questionnaire, you and your hospital will be part of this European-wide survey. It will take approximately 30 minutes to answer and you may need to consult other healthcare professionals to answer some of the questions. In return we will keep you informed of the results and outcome of this survey.
Your answers will be treated in the strictest confidence.
This research project is supported by Baxter Healthcare Ltd.

Please contact me, if you have comments or questions about any aspect of this work.

I am looking forward to hearing from you.

With kind regards,
Yours sincerely,

Bettina Klüttgens.

UNIVERSITY OF BATH

Bettina Klüttgens

Department of Pharmacy and Pharmacology
Bath BA2 7AY
England

Tel. +44-1225-323107
Fax. +44-1225-826114
E-Mail: prpbuk@bath.ac.uk

Bath, April 2001

Sehr geehrte ,

ich würde mich sehr darüber freuen, wenn Sie und Ihre Klinik an einer europäischen Studie zu Verfahrensweisen bei der parenteralen Ernährung von Kindern und Neugeborenen teilnehmen würden.

Ich forsche auf dem Gebiet der klinischen Pharmazie an der University of Bath, England. Ich arbeite zusammen mit Professor Graham Sewell, Professor für klinische Pharmazie an der Universität in Bath, und Tony Nunn, Leiter der Krankenhausapotheke am Alder Hey Children's Hospital in Liverpool.

Ziel dieser Studie ist die Beantwortung der Frage, wie die pädiatrische parenterale Ernährung in Europa gehandhabt wird, und ob eine Standardisierung bei verschiedenen Alters- oder Gewichtsgruppen möglich ist.

Mit der Beantwortung des beigefügten Fragebogens nehmen Sie und Ihre Klinik an dieser europaweiten Studie teil. Die Beantwortung des Fragebogens dauert etwa 30 Minuten, wobei Sie gegebenenfalls andere Kollegen konsultieren müssen, um einige der Fragen zu beantworten. Ihre Antworten werden selbstverständlich steng vertraulich bleiben.
Wenn Sie möchten, werden wir Sie über die Ergebnisse dieser Studie auf dem Laufenden halten.
Dieses Forschungsprojekt wird von der Firma Baxter Healthcare Ltd. unterstützt.

Bei Fragen oder Kommentaren zu allen Aspekten dieser Arbeit stehe ich Ihnen gerne jederzeit zur Verfügung.

Ich freue mich schon jetzt darauf, von Ihnen zu hören.

Mit freundlichen Grüßen

Bettina Klüttgens

UNIVERSITY OF BATH

Bettina Klüttgens

Department of Pharmacy and Pharmacology
Bath BA2 7AY
England

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Bath, avril 2001

Chèr ,

J'ai le plaisir de vous inviter, ainsi que votre établissement hospitalier, à participer à une importante enquête européenne sur les pratiques en nutrition parentérale néonatale et pédiatrique.

Je suis pharmacien chercheur à l'Université de Bath, en Angleterre. Je travaille en collaboration avec Graham Sewell, Professeur de Pharmacie à l'Université de Bath et Tony Nunn, Pharmacien chef à l'Hôpital des enfants Alder Hey de Liverpool.

L'objectif de cette enquête est d'évaluer les différents modes de nutrition parentérale pédiatrique en Europe et de déterminer s'il est possible de standardiser les pratiques en fonction du groupe d'âge et de poids des enfants.

Si vous et votre établissement hospitalier acceptez de prendre part à cette enquête conduite à l'échelon européen, nous vous demandons de répondre au questionnaire joint. Seules 30 minutes seront nécessaires pour le compléter, mais il se peut que vous deviez consulter vos professionnels de la santé pour répondre à certaines questions. Nous vous tiendrons informés en retour, des résultats et des conclusions de cette étude.
Votre réponse sera évidemment traitée confidentiellement.
Ce projet de recherche est financé par la société Baxter Healthcare Ltd.

Pour tout commentaire ou toute question sur l'un des aspects de ce travail, n'hésitez pas à me contacter à tout moment.
En vous remerciant par avance et dans l'attente de votre réponse, veuillez agréer l'expression de mes salutation distinguées.

Bettina Klüttgens.

UNIVERSITY OF BATH

Bettina Klüttgens

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England

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prpbuk@bath.ac.uk

Bath, April 2001

Egregi ,

Sarei molto lieta della vostra partecipazione e di quella degli ospedali in cui svolgete le vostre attività ad un'importante indagine europea sulla pratica della nutrizione parenterale neonatale e pediatrica.

Lavoro come ricercatrice presso la Facoltà di Farmacia dell'Università di Bath.

Collaboro con il prof. Graham Sewell, docente di Analisi dei farmaci presso questa Università e con il dott. Tony Nunn, Farmacista Capo presso l'Alder Hey Children's Hospital di Liverpool.

Lo scopo di questa indagine è di valutare le modalità di gestione della nutrizione parenterale in Europa e di individuare la possibilità di standardizzazione per diversi gruppi di età o di peso.

Rispondendo al questionario allegato, voi e il vostro ospedale parteciperete a questa indagine a carattere europeo. Il completamento del questionario richiede circa 30 minuti e, per rispondere ad alcune domande, potrà essere necessario consultare altri medici. In cambio, vi terremo informati dei risultati e dell'esito dell'indagine.

Le vostre risposte saranno trattate con il massimo della confidenzialità.

Questo progetto di ricerca è finanziato da Baxter Healthcare Ltd.

Sono a disposizione in qualsiasi momento per eventuali chiarimenti o commenti sui diversi aspetti del progetto.

Potere inviare il questionario anche via fax al numero: 0044-1225-826114

Restando in attesa di un gentile riscontro, invio
Cordiali saluti,

Bettina Klüttgens

UNIVERSITY OF BATH

Bettina Klüttgens

Department of Pharmacy and Pharmacology
Bath BA2 7AY
England

Teléfono +44-1225-323107
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Dirección de correo electrónico:
prpbuk@bath.ac.uk

Bath, April 2001

Querido :

Le agradecería mucho si usted y su hospital pudieran participar en un importante estudio europeo sobre la práctica de la nutrición parenteral con neonatos y niños.

Trabajo como farmacéutico de investigación en la Universidad de Bath y colaboro con Prof. Graham Sewell, Profesor de Práctica de Farmacia en la Universidad de Bath, y Dr. Tony Nunn, Jefe de Farmacia del Hospital infantil Alder Hey, en Liverpool.

El objetivo de este estudio consiste en evaluar la forma en la que se administra la nutrición parenteral pediátrica en Europa, así como en averiguar si existe potencial para realizar una estandarización en diferentes grupos de edad o peso.

Al rellenar el cuestionario adjunto, usted y su hospital formarán parte de este gran estudio europeo. Necesitará aproximadamente 30 minutos para responder a todas las preguntas y es posible que tenga que consultar a otros profesionales de asistencia sanitaria para responder a algunas de ellas. Por nuestra parte, nosotros le informaremos de los resultados y de las consecuencias de este estudio.
Este proyecto de investigación está apoyado por Baxter Healthcare Ltd.

Si tiene comentarios o preguntas acerca de algún aspecto de este trabajo, no dude en ponerse en contacto conmigo.

Quedo a la espera de sus noticias.

Sin otro particular le saluda atentamente,

Bettina Klüttgens.

European Practice in Paediatric Parenteral Nutrition

Pharmacy Practice Research Group
School of Pharmacy and Pharmacology
University of Bath

Bettina Klüttgens

Contact: prpbuk@bath.ac.uk
Department of Pharmacy and Pharmacology
University of Bath, BA2 7AY Bath, England

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UNIVERSITY OF BATH

PART ONE: Practice of parenteral nutrition

Section A: General information

1. How many neonatal/children's beds are there in your hospital?

Neonates .....

Children .....

2. How many paediatric patients receive intravenous nutrition on an **average** day in your hospital?

Neonates:	❑ 0-1	❑ 8-10	❑ 17-19
	❑ 2-4	❑ 11-13	❑ 20-25
	❑ 5-7	❑ 14-16	❑ >25
Children:	❑ 0-1	❑ 8-10	❑ 17-19
	❑ 2-4	❑ 11-13	❑ 20-25
	❑ 5-7	❑ 14-16	❑ >25

3. What is the job title of the person/persons involved in the decision making of parenteral nutrition treatment?

Prescribing .....

Preparation/Compounding .....

Monitoring .....

Administration .....

Purchase .....

Section B: Supply of parenteral nutrition

4. Is there a unit in your hospital that compounds parenteral nutrition?

   ❑ Yes ❑ No

5. Do you use guidelines for the prescribing of parenteral nutrition?

   ❑ Yes ❑ No

   If yes, which ones?

   .....

   .....

   .....

6. What ingredients are used for the compounding of parenteral nutrition in different age groups? Please specify which *manufacturers product* you use.

	Neonates	Children
Fat	.....	.....
Amino acid	.....	.....
Water-soluble Vitamins	.....	.....
Fat-soluble Vitamins	.....	.....
Trace elements	.....	.....

7. How is the fat emulsion supplied? *(Tick as many boxes as necessary)*

   Please specify the approximate percentages of patients receiving the different formulations.

	Neonates	Children
❑ Separately	.....%	.....%
❑ All-in-one	.....%	.....%

8. What is the policy about the addition of *vitamins* to parenteral nutrition in different age/weight groups:

a) On which day after introducing parenteral nutrition do you start including vitamins?

	Neonates	Children
Water-soluble vitamins	.....	.....
Fat-soluble vitamins	.....	.....

b) How many days per week do the patients receive vitamins?

	Neonates	Children
Water-soluble vitamins	.....	.....
Fat-soluble vitamins	.....	.....

9. What is the policy about the addition of *trace elements* to parenteral nutrition in different age/weight groups?

a) On which day after introducing parenteral nutrition do you start including trace elements?

Neonates ..... Children .....

b) How many days per week do the patients receive trace elements?

Neonates ..... Children .....

10. What is the *maximum shelf life* assigned to the compounded parenteral nutrition bag?

.....

11. Are filters used during the administration of parenteral nutrition?

❑ Yes, always ❑ Yes, sometimes ❑ No

12. Is some kind of light protection used during the *administration* of parenteral nutrition?

For the bag:	❑ Yes, always	❑ Yes, sometimes	❑ No
For the tubing:	❑ Yes, always	❑ Yes, sometimes	❑ No

13. What kinds of end-control are used for *every compounded individual* bag?

- ❑ None
- ❑ Visual check
- ❑ Weighing
- ❑ Osmolarity
- ❑ Electrolyte assay
- ❑ Sterility
- ❑ Other .....

14. Is parenteral nutrition for paediatric patients prepared on the ward?

❑ Yes, regularly ❑ Yes, rarely ❑ No

15. Are ingredients added to the nutrition solution on the ward?

❑ Yes, regularly (in approx. **more** than 20% of bags)	❑ Yes, rarely (in approx. **less** than 20% of bags)	❑ No
If *yes*, please specify the ingredient added on the ward:	If *yes*, please specify the ingredient added on the ward:	

Section C: Standardisation

16. Do you use *standard solutions* for some patients (i.e.: In-house batch production or commercially available ready-to-use solutions)?

- ❑ **Yes → Please answer questions 17 to 21 and continue with part 2 (page 8).**
- ❑ **No → Please go to question 22 (page 7) and continue with part 2 (page 8).**

17. Why did you decide to use standardised solutions for some patients?

.....
.....
.....

18. In which year were standard solution/solutions introduced?

.....

19. Where does the formulation for standardisation come from?

.....

(Please include a copy of the standard solutions used if possible.)

20. Are commercially available ready-to-use nutrition solutions used in your hospital?

❑ Yes, always ❑ Yes, sometimes ❑ No

If yes, which one/ones?

.....

21. In case standard solutions are produced in your hospital: What kinds of end-control are used ? *(Tick as many boxes as necessary)*

- ❑ None
- ❑ Visual check
- ❑ Weighing
- ❑ Osmolarity
- ❑ Electrolyte assay
- ❑ Sterility
- ❑ Other .....

Please go now to page 8

22. What are the reasons for the individual compounding of parenteral nutrition in your hospital?

.....
.....
.....
.....

23. Have any steps been taken towards standardising the parenteral nutrition for children and neonates?

❑ Yes ❑ No

If yes:
❑ for Neonates
❑ for Children

24. Would your hospital be prepared to use standardised solutions?

❑ Yes
If yes, why?
.....
.....
.....
.....
.....

❑ No
If no, why not?
.....
.....
.....
.....
.....

PART TWO: Standard solutions

The next pages show different options of nutrient concentration for five age/weight groups.

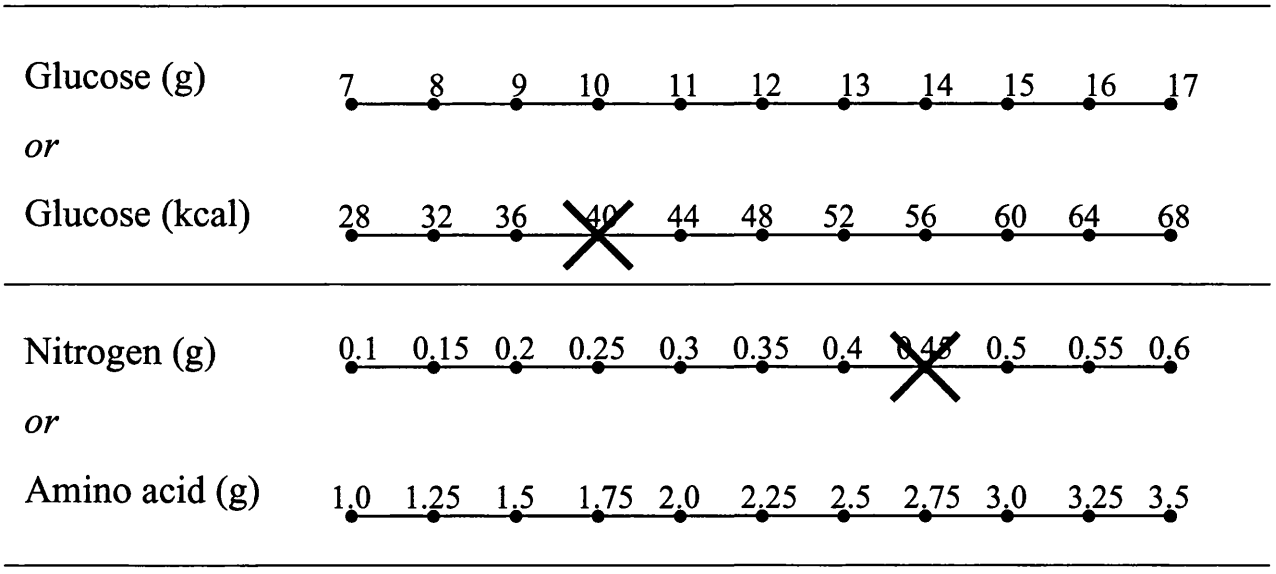
If you were to design a standard solutions for paediatric patients, which quantity of nutrients would you find most suitable for the majority (or a large part) of your patients for different age/weight groups?

Please cross one point on the line:

Example:

You can choose between *gram* of glucose or *kcal* of glucose, and between using grams of *nitrogen* or gram of *amino acid* :

Example:



1. Premature Neonates

Please suggest a standard solution for premature neonates.

Cross ONE point for each component.

	Requirements per kilogram per 24 hrs
Volume (mL)	80 90 100 110 120 130 140 150 160 170 180
Nitrogen (g)	0.1 0.15 0.2 0.25 0.3 0.35 0.4 0.45 0.5 0.55 0.6
or	
Amino acid (g)	1.0 1.25 1.5 1.75 2.0 2.25 2.5 2.75 3.0 3.25 3.5
Glucose (g)	7 8 9 10 11 12 13 14 15 16 17
or	
Glucose (kcal)	28 32 36 40 44 48 52 56 60 64 68
Fat (g)	0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0
Sodium (mmol)	1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0
Potassium (mmol)	0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0

Comments:.....

.....

.....

2. Neonates

Please suggest a standard solution for neonates.

Cross ONE point for each component.

	Requirements per kilogram per 24 hrs
Volume (mL)	80 90 100 110 120 130 140 150 160 170 180
Nitrogen (g)	0.1 0.15 0.2 0.25 0.3 0.35 0.4 0.45 0.5 0.55 0.6
or	
Amino acid (g)	1.0 1.25 1.5 1.75 2.0 2.25 2.5 2.75 3.0 3.25 3.5
Glucose (g)	7 8 9 10 11 12 13 14 15 16 17
or	
Glucose (kcal)	28 32 36 40 44 48 52 56 60 64 68
Fat (g)	0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0
Sodium (mmol)	1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0
Potassium (mmol)	0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0

Comments:.....

.....

.....

3. Children < 10 kg

Please suggest a standard solution for children < 10kg.

Cross ONE point for each component.

	Requirements per kilogram per 24 hrs
Volume (mL)	40 50 60 70 80 90 100 110 120 130 140
Nitrogen (g)	0.1 0.15 0.2 0.25 0.3 0.35 0.4 0.45 0.5 0.55 0.6
or	
Amino acid (g)	1.0 1.25 1.5 1.75 2.0 2.25 2.5 2.75 3.0 3.25 3.5
Glucose (g)	5 6 7 8 9 10 11 12 13 14 15
or	
Glucose (kcal)	20 24 28 32 36 40 44 48 52 56 60
Fat (g)	0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0
Sodium (mmol)	1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0
Potassium (mmol)	0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0

Comments:.....

.....

.....

4. Children 11-20 kg

Please suggest a standard solutions for children from 10-20 kg.

Cross ONE point for each component.

	Requirements per kilogram per 24 hrs
Volume (mL)	40 50 60 70 80 90 100 110 120 130 140
Nitrogen (g)	0.1 0.15 0.2 0.25 0.3 0.35 0.4 0.45 0.5 0.55 0.6
or	
Amino acid (g)	1.0 1.25 1.5 1.75 2.0 2.25 2.5 2.75 3.0 3.25 3.5
Glucose (g)	5 6 7 8 9 10 11 12 13 14 15
or	
Glucose (kcal)	20 24 28 32 36 40 44 48 52 56 60
Fat (g)	0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0
Sodium (mmol)	1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0
Potassium (mmol)	0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0

Comments:.....

.....

.....

5. Children 21-30 kg

Please suggest a standard solutions for children from 21-30 kg.

Cross ONE point for each component.

	Requirements per kilogram per 24 hrs
Volume (mL)	40 50 60 70 80 90 100 110 120 130 140
Nitrogen (g)	0.1 0.15 0.2 0.25 0.3 0.35 0.4 0.45 0.5 0.55 0.6
or	
Amino acid (g)	1.0 1.25 1.5 1.75 2.0 2.25 2.5 2.75 3.0 3.25 3.5
Glucose (g)	5 6 7 8 9 10 11 12 13 14 15
or	
Glucose (kcal)	20 24 28 32 36 40 44 48 52 56 60
Fat (g)	0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0
Sodium (mmol)	1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0
Potassium (mmol)	0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0

Comments:.....

.....

.....

Thank you for taking the time to complete this questionnaire.

If you wish, we will inform you about the results of this survey:

- ❑ Yes, please send results of this survey,
- ❑ No, please do not send results of this survey.

If you have any comments, queries, or suggestions, please do not hesitate to contact me.

Please include copies of standard formulations and nutritional recommendations you use, or other documents that you consider helpful in this survey.

Bettina Klüttgens

Please place your stamp here, if you wish.

APPENDIX 3:

South-West multicentre ethics committee: letter of acknowledgement of neonatal nutrition study

NHS

South West Multi-centre Research Ethics Committee

Ms Bettina Klüttgens
Department of Pharmacy and Pharmacology
University of Bath
Bath
BA2 7AY

The Lescaze Offices
Shinner's Bridge
Dartington
Devon
TQ9 6JE

Tel: 01803 861947
Fax: 01803 861914
Email: swmrec@sw-devon-ha.swest.nhs.uk

16 April 2002

Dear Ms Klüttgens

Re: International Audit of Parenteral Nutrition Intake in Neonates

As requested following e-mail communication and receipt of amended documents for the above audit, the South West MREC has considered them in an advisory capacity.

It has been noted that both the Protocol (Fourth Version 8 April 2002) and the Plan of Data Analysis (Third Version 8 April 2002) incorporate the suggestions made by the South West MREC regarding making it explicit that the project is an audit.

The Committee believes that the project as proposed in the documents received does not fall within the current remit of a NHS Research Ethics Committee and, accordingly, there is not a requirement for it to be subject to ethical review.

Yours sincerely

Barrie Behenna
Chairman

APPENDIX 4:

Invitation and reply form for UK participants of neonatal nutrition study

Bettina Klüttgens
Research Pharmacist

E-mail: prpbuk@bath.ac.uk

Clinical Pharmacy & Pharmacy Practice Research

UNIVERSITY OF BATH

Department of Pharmacy and Pharmacology
Bath BA2 7AY United Kingdom
Telephone +44 1225 384142
Facsimile +44 1225 386114

22nd March 2002

Dear ,

International Non-Interventional Survey of Parenteral Nutrition Intake in Neonates

I work as a Research Pharmacist at the University of Bath.

I would like to invite you and your neonatal team to take part in this international survey, which will investigate the potential for standardization of neonatal parenteral nutrition.
This survey is part of a three-year PhD project studying clinical and pharmaceutical aspects of paediatric parenteral nutrition.

If you decide to take part in this survey, your time commitment or that of your staff will be minimal, as I will collect the data, and you will be informed about the results of the survey.
All information collected about your patients will be anonymous and kept in secure facilities.

A copy of the survey protocol has been sent to the South West Multicentre Ethics Committee.

Please send your reply before the **19th of April**, using the enclosed form and free return envelope.

Please contact me if you would like to find out more about the study, or if you have any questions.

I am looking forward to hearing from you.

Yours sincerely,

Bettina Klüttgens

International Non-Interventional Survey of Parenteral Nutrition Intake in Neonates

☐ Yes, I would like to take part in the survey about neonatal parenteral nutrition

Name: _____

Hospital: _____

_____

Phone: _____

E-mail: _____

Date: __ / __ / _____ Signed: _____

APPENDIX 5:

Confidentiality agreement for neonatal nutrition study

CONFIDENTIALITY AGREEMENT

THIS AGREEMENT is made on the day of 2002

BETWEEN

1 **THE UNIVERSITY OF BATH** of Claverton Down Bath BA2 7AY ('the University') and

2
whose address office is at ('the Recipient')

BACKGROUND

A The University possesses valuable confidential information relating to a research project to be carried out by the University's Department of Pharmacy and Pharmacology under the supervision of Ms Bettina Kluettgens ('the Project'). The project will be carried out by means of a study entitled 'International Audit of Parenteral Nutrition Intake in Neonates' ('the Study').

B The Recipient wishes to review confidential information relating to the Project and the Study with a view to deciding whether to take part in the Study and the University is willing to disclose such confidential information to the Recipient on the terms and conditions set out in this Agreement

IT IS agreed:-

1 **IN** this Agreement:-

'the Information' shall mean all and any information relating to the Project and/or the Study obtained directly or indirectly by the Recipient from the University, whether in written or oral or any other form and including without limitation data, methods, techniques, specifications and any information relating to these items

2 **THE** Recipient hereby undertakes to keep the Information confidential and not to disclose the Information to any third party except as provided by this Agreement or with the University's prior written consent nor make any use whatsoever of the Information except for the sole purpose of considering whether to participate in the Study as outlined above and in order to obtain local ethics committee approval. The provisions of this Clause shall extend (without limiting its generality) to any information, which comes to the knowledge of the Recipient as a result of any visit to the University's premises

3 **THE** Recipient may disclose such parts of the Information as may be necessary to those of its employees and agents or local ethics committee personnel who need to know the same for the purposes of this Agreement, but shall ensure that such employees, agents and personnel are aware of and abide by the provisions of this Agreement (and shall if requested by the University obtain from all such employees, agents and personnel a written undertaking in terms to be approved by the University to be bound by like obligations as to confidentiality as are accepted by the Recipient)

4 **THE** provisions of this Agreement shall not apply to information:-

(a) which at the time of disclosure is already in the public domain or subsequently comes into the public domain otherwise than by any act or omission of the Recipient, its employees, servants or agents

(b) which the Recipient can show by written records was already rightfully in its possession at the date of disclosure

(c) which the Recipient can show by written records was subsequently to the date of disclosure obtained from an independent third party under no obligation of confidence to the University

5 **IF** the Recipient decides that they do not wish to participate in the Study or to enter into any other agreement with the University in respect of the subject matter of the Information, they shall promptly deliver up to the University all Information and all copies or embodiments of it in their possession or in that of its servants, agents or employees and shall in any event do so within fourteen days of any request by the University in writing

6 **THIS** Agreement shall not be construed as granting to the Recipient any licence or other rights to use the Information except for the purposes specifically set out herein

7 **THIS** Agreement shall endure for a period of 7 years from the disclosure to the Recipient of the Information and be subject to English Law and to the non-exclusive jurisdiction of the High Court of Justice in England

SIGNED by .....
duly authorised by
and on behalf of
THE UNIVERSITY OF BATH

SIGNED by .....
duly authorised by
and on behalf of
The Recipient

APPENDIX 6:

Protocol and plan of statistical analysis for neonatal nutrition study

UNIVERSITY OF BATH

International Audit of Parenteral Nutrition Intake in Neonates

Project Manager: **Bettina Klüttgens**
Department of Pharmacy and Pharmacology
University of Bath
Bath, BA2 7AY
United Kingdom
Phone: +44 1225 384142
Mobile: +44 7968594030
Fax: +44 1225 386114
E-mail: prpbuk@bath.ac.uk

Sponsored by	**Baxter Europe Medication delivery**
Contact for Sponsors	**Hervé Toullec** **BAXTER S.A.** **6, Avenue Louis-Pasteur – B.P. 56** **78311 – Maurepas Cedex – France**
Statisticians	**Dr. Gordon Taylor** **University of Bath** **Wolfson Centre** **Royal United Hospital** **Bath BA1 3NG - UK** **Dr. Alexia LeBrun** **R&D Parenteral Nutrition Baxter** **6, Avenue Louis Pasteur** **78311 – Maurepas Cedex – France**
Medical Experts (centres)	**Prof. Jacques Rigo** **Liege, Belgium** **Dr. Virginie Colomb** **Paris, France** **Dr. Uwe Ewald** **Uppsala, Sweden** **Dr. Paivi Luukkainen** **Helsinki, Finland** **Prof. Agostino Pierro** **London - United Kingdom** **Prof. Berthold Koletzko** **Munich – Germany** **Tony Nunn** **Liverpool – United Kingdom**

Table of Content

1 Abbreviations and Definitions

1.1 Abbreviations

PN	Parenteral Nutrition
EN	Enteral Nutrition
PICC	Peripherally Inserted Central Catheter
TNA	Total Nutrient Admixture

1.2 Definitions

Parenteral Nutrition	Infusion of a mixture of at least amino acids and glucose
Neonate	Newborn baby from birth to 27 days of age (ICH guidelines)
Binary solution	Mixture of amino acids and glucose, and sometimes electrolytes and vitamins
TNA	Total Nutrient Admixture: Lipid is infused together with the binary solution as pre-mixed solution ('All-in-One')
Filter	Filter used close to the patient when administering the parenteral nutrition solution
Day of PN	Number of days since parenteral nutrition started for the first time

2 Audit Period

Piloting: April 2002

Start of data collection: May 2002

End of data collection: July 2002

3 Introduction

PN is a life saving treatment, especially in the neonatal patient group. A recent audit found that as many as 43% of hospitals have introduced some form of standardization for their paediatric PN (unpublished data). The main reasons for this are pharmaceutical and economical. Several hospitals have published their experience with the use of neonatal standard feeding solutions [1-4]. Currently, no commercial feeding solution is available for neonates, although some commercial products are suitable for children.

The increase in use of standardized PN has not been accompanied by an increase in knowledge regarding the safety of such treatment. It is therefore of great importance to investigate the risks and benefits of standardizing PN for neonates. Beecroft and co-workers have investigated the adherence of prescribers to the recommendations of a computer program [5]. They found that 82% of prescriptions deviated from the recommendations, but the authors estimate that up to two third of prescriptions could be given as standardized feed with an adjusted regimen.

4 Audit Objectives

4.1 First Objective

Investigate prescribing practice in neonatal centres, in terms of variability of nutrition composition and differences between prescribed and administered PN.

4.2 Second Objective

Investigate the potential for introducing standard PN solutions for neonates, by means of comparing prescribed and delivered PN to the following standard solution (in 100 mL):

Glucose	12 g
Amino acid	2.5 g
Lipid	2 g
Na	1.5 mmol
K	1.5 mmol

This standard has been developed as a combination of information from an international audit (unpublished data), and subsequent discussions with specialists in the field of neonatal PN.

5 Audit Plan

5.1 Number of Observations

One observation is defined as the nutrition prescribed and received by one patient in 24 hours.

5.1.1 Observations per Centre

For each centre, data are collected for a period of *14 days*, according to the inclusion/exclusion requirements (see 5.2).

Each centre includes a *minimum* of 5 patients.

A *minimum* of 15 observations amongst all patients is collected.

If less than 15 total observations have been collected or less than 5 patients been included after 14 days, the data collection continues until both requirements have been met.

5.1.2 Choice and Number of Centres

Centres will be chosen in two different ways:

In several European countries, hospitals with renowned expertise in neonatal nutrition are invited to participate. These centres will undertake the audit *prospectively* and a local data collector is employed.

In the UK, in addition to the centres described above, 5-8 hospitals are selected in a randomised way to participate *retrospectively*. All UK hospitals are invited, providing they treat at least 300 neonatal patients in an average year (Source: Neonatal Nurses Association Yearbook 2001), and providing their records will allow a retrospective data collection. Data will be collected by the project manager.

5.2 Patient Population

Neonates receiving parenteral nutrition

5.2.1 Inclusion Criteria

Neonates receiving *at least approximately half of daily nutrition volume* from PN for any clinical reason (According to ICH guidelines, neonates are no older than 27 days)
Minimum requirement for inclusion is the infusion of glucose and amino acids.

5.2.2 Exclusion Criteria

More than approximately half of nutrition volume from EN and/or oral feeding
Patient is more than 27 days old
Infusion of glucose alone

5.3 Data Collection

Three different forms are used for data collection:
Information about the Centre: This form (one page) asks for general information about the audit centre and only needs to be filled in once at the start of data collection.
Information about Subject: This form (one page) asks for general information about the patient and only needs to be filled in once when the patient is enrolled.
Information about Nutrition: This form (two pages) collects data about PN prescription and PN/EN administration and needs to be filled in for every day of parenteral nutrition.

5.3.1 Audit Centre details

Country; Name of hospital
Total number of neonatal beds
Number of neonatal intensive care beds
Average number of surgical neonates per year
Average number of neonatal patients ≤1500g birth weight per year
Use of administration filters (Binary solution, lipid, both, no filter used)
Information about data collector and signature

5.3.2 Patient details

Patient identification number

Gender; Birth weight; Date of Birth; Gestational age;

Apgar Score (1 min/5 min)

Date of first PN prescription (if PN has been interrupted and restarted, please give the restarting date)

5.3.3 Clinical details

Date of observation

Body weight at date of observation

Venous access (Central, peripheral, PICC)

Clinical situation/history: Surgery, fluid restriction, Congenital malformation, metabolic disorder, sepsis (significant), Organ failure leucopoenia, other

5.3.4 Nutrition Prescription

For PN:

Parenteral Nutrition given as standard solution or not

Lipid administration (Separately or as TNA)

Lipid solution (20%; 30%)

Volume (Lipid emulsion; binary solution; ternary solution; total volume)

Amount of glucose, amino acids, sodium and potassium

5.3.5 Nutrition Administered

Volume of PN (Lipid emulsion; binary solution; ternary solutions; total volume)

Volume of EN

Volume of breast milk

6 Organisation of Audit

6.1 Centres of Expertise

In the centres of expertise throughout Europe, the data collection will take place in a prospective way by a local collector.

At the end of every day, the data collector will send a fax to the project manager, including data collection forms about new patients and all nutrition report forms of the day. At the end of the 14 days of audit (or more days if needed), the data collector signs the document and the complete folder will be sent by post to the project manager. Before the start of the audit, each hospital will be sent a data collection folder, which will contain the following items:

- Cover sheet: Data collection form for audit centre
- 20 plastic wallets with the data collection form for patients as cover sticker and one data collection form for nutrition inside
- 30 spare data collection forms for nutrition information
- Fax cover sheet for daily faxes to project manager
- Copy of all relevant documents

6.2 Other centres

In the other centres in the UK, data will be collected by the project manager in a retrospective way. A similar folders as mentioned in 6.1 will be used.

7 Plan of Data Analysis

Please refer to separate document.

8 References

1. Aldamiz-Echevarria Azuara L, Bachiller Cacho MP: Parenteral nutrition standard in the newborn. An Esp Pediatr 43:203, 1995
2. Digel S: Standard nutrition solutions for neonates and premature children. Krankenhauspharmazie 19:62-66, 1998
3. Willimsky S, R. K, Geier N: Computergestuetzte standardisierte parenterale Ernahrung in der Neonatologie. Monatsschr Kinderheilkd 148:713-718, 2000
4. Gow GL, Middlehurst GC: Standard total parenteral nutrition for a special care baby unit. Pharmaceutical Journal 255:740-742, 1995
5. Beecroft C, Martin H, Puntis JWL: How often do parenteral nutrition prescriptions for the newborn need to be individualized? Clin. Nutr. 18:83-85, 1999

International Audit of Parenteral Nutrition Intake in Neonates

Plan of Data Analysis

1 Definition: Criteria of Analysis

Data collected from European expert centres will be analysed separately from the UK based data.

Feedback will be sent to each participating centre about their results.

1.1 Primary analysis

Quantification of differences between prescribed and administered parenteral nutrition

The volumes of prescribed and administered parenteral nutrition will be compared for each observation, with regard to:

- Binary solution volume
- Lipid emulsion volume
- TNA volume

If in more than 50 cases the volume administered is below 80% of the prescribed volume of parenteral nutrition, those cases will be analysed separately according to the nutrition administered.

1.2 Secondary analysis

Parenteral nutrition prescription data will be compared to standard solution.

The standard solution will be used as defined in the study protocol and the following ranges will be applied to all components of the nutrition solution:

Component of PN	Standard (100mL)	Range 80-120%	Range 70-130%
Glucose (g)	12	9.6-14.4	8.4-15.6
Amino acids (g)	2.5	2-3	1.7-3.3
Lipid (g)	2	1.6-2.4	1.4-2.6
Sodium (mmol)	1.5	1.2-1.8	1-2
Potassium (mmol)	1.5	1.2-1.8	1-2
Level of agreement between prescription & standard		Good	Moderate

The nutrition solution will be compared to the standard with regard to all five components:

- Glucose, Amino acids, Lipid, Sodium, Potassium

Analysis will also be performed on combinations and single components:

- Macronutrients (Glucose, Amino acids, Lipid)
- Binary solutions (Glucose, Amino acids)
- Glucose only
- Amino acids only
- Lipid only
- Sodium only
- Potassium only

2 Sub-populations

The data will be analysed according to several sub-populations.

Case will be split into:

SUB-POPULATION	NUMBER OF GROUPS
Type of centre	1. Expert 2. Other
Country	One expert centre per country
Birth weight	1. < 1500g 2. >= 1500g
Day of PN	1. 1st Day 2. 2nd-3rd Day 3. 4th-6th Day 4. > 7th Day
Type of nutrition	1. Full PN (>80% of kcal from PN) 2. Partial PN (50-80% of kcal from PN)
Venous access	1. Peripheral 2. Central / PICC
Clinical situation	1. Ventilation: Yes 2. UV-Therapy: Yes 3. Body temperature >38°C
Clinical factors	1. Fluid restriction 2. Critically ill 3. Post-operative 4. Other

3 Summary of Statistical Plan

	All	Macronutrients	Binary solution	Glucose	Amino acids	Lipid	Sodium	Potassium
All cases	x	x	x	x	x	x	x	x
Type of centre	x	x	x			x	x	x
Country	x							
Birth weight	x	x	x				x	x
Day of PN	x		x			x		
Type of nutrition	x							
Venous access	x	x						
Clinical situation	x	x						
Pathologies	x	x						
Vol. administered*	x	x	x			x		

*See 1.2

4 Descriptive Statistics

4.1 Audit centre

Audit centres will be characterised by the number of total beds, number of neonatal beds and number of yearly neonatal admissions.

Quantification of the use of administration filters and the type of filers used

4.2 Subjects

Distribution of male versus female subjects

Mean and standard deviation of birth weight

Mean and standard deviation of gestational age

Mean and standard deviation of Apgar score at 1min/5min

4.3 Sub-population

All sub-populations will be characterised in terms of the number of cases in each of the groups.

APPENDIX 7:

Data collection forms and guidance for use of data collection forms

International audit of parenteral nutrition intake in neonates

INFORMATION ABOUT THE AUDIT CENTRE

This form is only to be filled in ONCE for each centre

Country _____

Name of hospital _____

_____

Total number of neonatal beds |_ _|_ _|

Number of designated neonatal intensive care beds |_ _|_ _|

Average number of surgical neonates per year |_ _|_ _|_ _|

Average number of neonates ≤1500g birth weight treated per year |_ _|_ _|_ _|

Use of *administration* filters *(tick as many boxes as necessary)*

- ❑ Binary Solution
- ❑ Lipid Emulsion
- ❑ Ternary nutrient admixture
- ❑ No filters are used

Project Manager	Bettina Klüttgens University of Bath E-mail: prpbuk@bath.ac.uk	Phone: +44 1225 384142 Mobile: +44 7968594030 Fax: +44 1225 386114

Data Collector

Title *(circle)* Mr./Mrs./Ms./Dr./Prof.

First Name _____

Surname _____

Telephone number _____

Signature of data collector:

_____

Date |_ _|_ _|/|_ _|_ _|/2002

INFORMATION ABOUT THE PATIENT

Patient identification number |_ _| - |_ _| - |_ _|_ _|

ONLY include patient:

- No older than 27 days
- Receiving at least intravenous glucose *and* amino acids

This form is only to be filled in ONCE for each patient

Gender	❑ Male ❑ Female	Date of Birth	|_ _|_ _|/|_ _|_ _|/2002
Birth weight	|_ _|_ _|_ _|_ _| g	Apgar 1min	|_ _|
Gestational age	|_ _|_ _|weeks	Apgar 5min	|_ _|

Date of first parenteral nutrition * |_ _|_ _|/|_ _|_ _|/2002

* In *this* sequence of PN. If the patient has received PN before, but interrupted the treatment, please give the *restarting date*.

Patient history *(please tick as many boxes as appropriate)*

❑ Surgery	❑ Sepsis (significant)
❑ Fluid restriction	❑ Organ failure
❑ Congenital malformation	❑ Leucopoenia
❑ Metabolic disorders	❑ Other _____ (Please specify)

NUTRITION INFORMATION

If patient receives less than approx. half of total nutrition volume from parenteral nutrition

→ All information relates to prescribed/administered nutrition **in 24 hours**

Date of observation |_ _|_ _|/|_ _|_ _|/2002

Body weight at day of observation |_ _|_ _|_ _|_ _|_ _| g

Venous access

- ❑ Central line (tip of catheter ends in a central vein/right atrium)
- ❑ Peripheral line (tip of catheter ends in a peripheral vein)

Total fluid administered in 24 hours
(**Including** enteral and parenteral nutrition volumes, flushes, drugs clear fluids; **excluding** blood products)

|_ _|_ _|_ _|_ _|_ _| mL

PARENTERAL NUTRITION PRESCRIPTION

Prescription is for standard bag ❑ Yes ❑ No
(Only if standard given unchanged)

Lipid given separately ❑ Yes ❑ No

Lipid given in form of ❑ 20% ❑ 30% emulsion

Volume Lipid Emulsion |_ _|_ _|•|_ _| mL

Volume Binary solution |_ _|_ _|_ _|•|_ _| mL
or
Volume Tertiary solutions |_ _|_ _|_ _|•|_ _| mL

Total volume |_ _|_ _|_ _|•|_ _| mL

Amino acids |_ _|_ _|•|_ _| g	Sodium |_ _|_ _|•|_ _| mmol
Glucose |_ _|_ _|•|_ _| g	Potassium |_ _|_ _|•|_ _| mmol
Lipid |_ _|•|_ _| g	

PARENTERAL NUTRITION ADMINISTERED

Volume Lipid Emulsion |_ _|_ _|•|_ _| mL

Volume Binary solution |_ _|_ _|_ _|•|_ _| mL
or
Volume Tertiary solutions |_ _|_ _|_ _|•|_ _| mL

Total volume |_ _|_ _|_ _|•|_ _| mL

ENTERAL/ORAL NUTRITION ADMINISTERED

Enteral Product

Name _____ Volume |_ _|_ _|_ _|•|_ _| mL

Breast milk |_ _|_ _|_ _|•|_ _| mL

International Audit of Parenteral Nutrition Intake in Neonates

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Sodium (mmol)	1.5	1.2-1.8	1-2
Potassium (mmol)	1.5	1.2-1.8	1-2
Level of agreement between prescription & standard		Good	Moderate

Data will also be compared to currently used standard solutions and to current recommendations of nutritional intake.

The nutrition solution will be compared to the standard with regard to all five components:

- Glucose, Amino acids, Lipid, Sodium, Potassium

Analysis will also be performed on combinations and single components:

- Macronutrients (Glucose, Amino acids, Lipid)
- Binary solutions (Glucose, Amino acids)
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- Amino acids only
- Lipid only
- Sodium only
- Potassium only

2 Sub-populations

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Country	One expert centre per country
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Day of PN	1. 1st Day 2. 2nd-3rd Day 3. 4th-6th Day 4. > 7th Day
Type of nutrition	1. Full PN (>80% of nutrition volume from PN) 2. Partial PN (50-80% of nutrition volume from PN)
Venous access	1. Peripheral 2. Central / Peripherally inserted Central Catheter
Clinical factors	To be determined

3 Summary of Statistical Plan

	All	Macronutrients	Binary solution	Glucose	Amino acids	Lipid	Sodium	Potassium
All cases	x	x	x	x	x	x	x	x
Type of centre	x	x	x			x	x	x
Country	x							
Gestational age	x	x	x				x	x
Day of PN	x		x			x		
Type of nutrition	x							
Venous access	x	x						
Pathologies	x	x						
Vol. administered*	x	x	x			x		

*See 1.2

4 Descriptive Statistics

4.1 Audit centre

Audit centres will be characterised by the number of surgical beds, number of neonatal intensive care beds and number of yearly neonatal admissions < or = 1500g.
Quantification of the use of administration filters and the type of filers used

4.2 Subjects

Distribution of male versus female subjects
Mean and standard deviation of birth weight
Mean and standard deviation of gestational age
Mean and standard deviation of Apgar score at 1min/5min

4.3 Sub-population

All sub-populations will be characterised in terms of the number of cases in each group.

APPENDIX 8:

Electronic data collection tool for neonatal nutrition study (Microsoft Access file – 2.7 MB)

Directions for use:

Insert disk into appropriate drive

Open file 'NeonatalNutritionDataCollectionTool'

Data entry frames open automatically

Examples of electronic data collection tool

PARENTERAL NUTRITION IN NEONATES

DATA COLLECTION TOOL

Main Menu

ENTER NEW CENTRE

ENTER NEW PATIENT

ENTER OBSERVATION

HELP

Click on button to open window

New Centre

Centre ID Number [ ] ?

Country [ ]

Hospital [ ]

Filters used [ ] ?

Data Collector [ ]

Phone number [ ]

Total number of neonatal beds [ ]

Number of designated intensive care beds [ ]

Average number of surgical patients per year [ ]

Avarage number of neonatal patients <1500g birth weight per year [ ]

Back to Main Menu

New Patient

ONLY include patients no older than 27 days, and who receive at least amino acids and glucose

Patient ID Number [ ] ?

Gender [ ]

Date of Birth [ ]

Birth Weight [ ] g

Gestational age [ ] weeks

Date of first PN [ ] *

*In this sequence of PN. If the patient has received PN before, but interrupted the treatment, please give the restarting date.

Apgar 1min [ ]

Apgar 5min [ ]

Patient History

- ☐ Surgery
- ☐ Fluid restriction
- ☐ Congenital malformation
- ☐ Metabolic disorders
- ☐ Sepsis (significant)
- ☐ Organ failure
- ☐ Leucopoenia

Other: [ ]

Back to Main Menu

New Observation

Observation ID Number

[ ] [?]

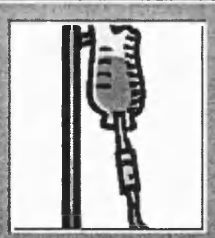
General Information

Date [ ]

Body weight [ ] g

Venous access [ ]

Total volume administered [ ] mL



Back to Main Menu

Prescription

[ ] Standard solution

[ ] Lipid separately

Lipid emulsion [ ]

Volume Lipid [ ] mL

Volume Binary [ ] mL

Volume Tertiar [ ] mL

Volume Total [ ] mL

Amino acids [ ] g

Glucose [ ] g

Lipids [ ] g

Sodium [ ] mmol

Postassium [ ] mmol

Nutrition Administered

Volume Lipid [ ] mL

Volume Binary [ ] mL

Volume Tertiary [ ] mL

Volume Total [ ] mL

Enteral/Oral Nutrition Administered

Enteral Product [ ]

Enteral Volume [ ] mL

Breast milk [ ] mL

APPENDIX 9:

Validation certificate for class 2 aseptic preparation cabinet

Customer's Name and Address

Contact M. Hough 01225 786727

Co. Name BATH UNI Dept

Address BATH

Call Ref. No: 217900

Contract No: 2742

BIOQUELL service
Walworth Road, Andover
Hampshire SP10 5AA United Kingdom
Tel: +44 (0)1264 835800
Fax: +44 (0) 1264 835801
E-mail: support@bioquellservice.com
Web: www.bioquellservice.com

A division of BIOQUELL UK Ltd
Registered No. 2520270

SERVICE REPORT No. A 217808

Customer Ord. No:

Purpose of Visit: CONTRACT SERVICE 1/2/3/4 ~~COMMISSIONING~~ ~~GENERAL REPAIR~~ *(Delete as necessary)*

Equipment CLASS II BIOHAZ. Model No: AC Date Commenced: 25/2/03 ~~WE / Bank Hol / Yes/No~~

Location: 5L3 3.21 Serial No: MC4607-1 Date Completed: 25/2/03 ~~WE / Bank Hol / Yes/No~~

Expenses Parking: Cause Code: Repair Code:

Unit status: Complete / ~~incomplete~~	Arrival time: 1500	Travelling Hours: 1¼
W/O status: ~~Complete~~ / incomplete	Departure time: 1600	Total Hours on Site: 1

1. CABINET FUNCTIONS

airflow indications	✓	indicator bulbs	✓
antiblow-back device	✗	fans	✓
alarms	✓	run on timer	✗
formalin unit	✗	gas solenoid	✗
lighting level (lux)	✓	UV lights (uw/cm3)	✗
sound level (dba)	✓	earth leakage (mA)	✗

2. PRE-FILTERS

size N/A changed/serviceable

3. PRESSURE DIFFERENTAILS

pre-filters Pa N/A HEPA filter Pa

work zone Pa

FAN SPEED SETTINGS

Exhaust 2 Recirc 3

5. FILTER INTEGRITY BS.3928 DOP

equipment FT8000 calibrated 8/2

Main HEPA		% penetration
Exhaust HEPA	< .003	% penetration
Downflow HEPA	< .003	% penetration
Outflow HEPA		% penetration
Inflow HEPA	< .003	% penetration

Comments:

Exact Copy

Signature [signature] Date 06/03/03

6. AIRFLOW MEASUREMENTS (Metres per second)

equipment used ANE calibrated 3/2

Test positions and airflow rates

MAIN AVG ↓ 0.40 m/s. EXHAUST

0.39	0.37	0.37	0.37
0.39	0.41	0.43	0.43

~~inflow through glove ports~~ LH RH

~~exhaust volumes m³/sec~~

INFLOW ~~calculated from exhaust~~ AVG 0.60 m/s.

7. PARTS USED

QTY	Part No.	Description
		NONE

Service/Tests as indicated above and overleaf carried out and conform to requirements unless otherwise stated:

Service Engineer Signature [signature] / M.N.P.

Authorised Customer Signature (Agreeing to statements contained in this report)

BSI REGISTERED FIRM Q11436

Name and Position

Signature [signature]

❑ White Copy (Customer Copy) ❑ Blue and Green Copies (Office Copies) ❑ Yellow Copy (Service Engineers Copy)

APPENDIX 10:

Calibration certificates for 20 µL, 100 µL, 200 µL, and 1000 µL pipettes

ANACHEM

Anachem Ltd. Anachem House, Charles Street, Luton, Bedfordshire, LU2 0EB, U.K.

Date Printed: 10-Feb-2003

CALIBRATION

ANACHEM CALL NUMBER: 109610

ORDER DETAILS

Calibration Date: 10-Feb-2003
Account/Customer: 02009 UNIVERSITY OF BATH
Contact: UNIVERSITY OF BATH

Ave Room Temp: 21.0 deg.C
Ave Water Temp: 21.0 deg.C
Technician: Liquid Handling Dept
Air Pressure: 1005hPa
Z Factor: 1.0031µL/mg
Humidity: 45.9%

PIPETTE DETAILS

Model: P20
Serial No: T55103N

Thermometer: TH16
Barometer: AB1
Balance: X
Balance Ref: 1119493182
Tips used: Gilson D200
Cust Order: SH462154-0
Cust Ref: SARAH ROBERTS
End User:

CALIBRATION DETAILS

Vol./Spec Code	2.000	(G7)	20.000	(G9)
Weighing 1 (mg)	1.970	(pass)	19.960	(pass)
Weighing 2 (mg)	2.000	(pass)	19.960	(pass)
Weighing 3 (mg)	1.990	(pass)	19.970	(pass)
Weighing 4 (mg)	1.990	(pass)	19.950	(pass)
Mean Wgt (mg)	1.988		19.960	
Mean Vol (µL)	1.994	(pass)	20.022	(pass)
Abs Inacc. (µL)	-0.006	(pass)	0.022	(pass)
Rel Inacc. (%)	-0.300	(pass)	0.110	(pass)
Abs SD (µL)	0.013	(pass)	0.008	(pass)
CV%	0.652	(pass)	0.040	(pass)
OVERALL STATUS		PASS		PASS

SERVICING DETAILS

Spares Code		Qty Used
T/HOLDER	H23353	1
PISTON	H23845	1

6 MONTH SERVICE WARRANTY

Technicians Signature .....

10 AUG 2003

Warranty Expiry Date .....

Specification Information:

Spec Code	Min Vol (µL)	Max Vol (µL)	Abs SD (µL)	CV%
G7	1.9	2.1	<= 0.030	<= 1.500
G9	19.8	20.2	<= 0.060	<= 0.300

Values Exclude Environmental Adjustment

Produced from computerised Liquid Handling System - (C) Anachem Ltd 1998 V6.1g

Telephone: +44 (0)1582 745061 Fax: +44 (0)1582 745130 www.anachem.co.uk email: lhlab@anachem.co.uk

Regd. Office: 20 Charles Street, Luton, Bedfordshire LU2 0EB Registration N°: 974301 England V.A.T. Registration N°: 196 2842 29

The calibration check was carried out using the gravimetric method as stipulated by the manufacturer, with weights that are traceable to the National Physical Laboratory.

LIQUID HANDLING

ANACHEM

Anachem Ltd. Anachem House, Charles Street, Luton, Bedfordshire, LU2 0EB, U.K.

Date Printed: 17-Jan-2003

CALIBRATION

ANACHEM CALL NUMBER: 109118

ORDER DETAILS		PIPETTE DETAILS	
Calibration Date:	17-Jan-2003	Model:	P100
Account/Customer:	02009 UNIVERSITY OF BATH	Serial No:	T62823K
Contact:	UNIVERSITY OF BATH	Thermometer:	TH16
Ave Room Temp:	21.0 deg.C	Barometer:	AB1
Ave Water Temp:	21.0 deg.C	Balance:	Y
Technician:	Liquid Handling Dept	Balance Ref:	11902938
Air Pressure:	998hPa	Tips used:	Gilson D200
Z Factor:	1.0031µL/mg	Cust Order:	SH462154-0
Humidity:	47.0%	Cust Ref:	SARAH ROBERTS
		End User:	

CALIBRATION DETAILS

Vol./Spec Code	20.000	(G10)	100.000	(G12)
Weighing 1 (mg)	19.900	(pass)	99.730	(pass)
Weighing 2 (mg)	19.930	(pass)	99.580	(pass)
Weighing 3 (mg)	19.950	(pass)	99.720	(pass)
Weighing 4 (mg)	20.010	(pass)	99.760	(pass)
Mean Wgt (mg)	19.947		99.698	
Mean Vol (µL)	20.009	(pass)	100.007	(pass)
Abs Inacc. (µL)	0.009	(pass)	0.007	(pass)
Rel Inacc. (%)	0.045	(pass)	0.007	(pass)
Abs SD (µL)	0.047	(pass)	0.080	(pass)
CV%	0.235	(pass)	0.080	(pass)
OVERALL STATUS		PASS		PASS

SERVICING DETAILS

Spares Code		Qty Used
O/RING	400067	1
T/HOLDER	H44602	1
SEAL	H44604	1

6 MONTH SERVICE WARRANTY

Technicians Signature ..... Warranty Expiry Date 17 JUL 2003

Specification Information:	Spec Code	Min Vol (µL)	Max Vol (µL)	Abs SD (µL)	CV%
	G10	19.65	20.35	<= 0.100	<= 0.500
	G12	99.2	100.8	<= 0.150	<= 0.150

Values Exclude Environmental Adjustment

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Regd. Office: 20 Charles Street, Luton, Bedfordshire LU2 0EB Registration N°: 974301 England V.A.T. Registration N°: 196 2842 29

The calibration check was carried out using the gravimetric method as stipulated by the manufacturer, with weights that are traceable to the National Physical Laboratory.

LIQUID HANDLING

ANACHEM

Anachem Ltd. Anachem House, Charles Street, Luton, Bedfordshire, LU2 0EB, U.K.

Date Printed: 17-Jan-2003

CALIBRATION

ANACHEM CALL NUMBER: 109118

ORDER DETAILS		PIPETTE DETAILS	
Calibration Date:	17-Jan-2003	Model:	P200
Account/Customer:	02009 UNIVERSITY OF BATH	Serial No:	T69850K
Contact:	UNIVERSITY OF BATH	Thermometer:	TH16
Ave Room Temp:	21.0 deg.C	Barometer:	AB1
Ave Water Temp:	21.0 deg.C	Balance:	T
Technician:	Liquid Handling Dept	Balance Ref:	1117473705
Air Pressure:	998hPa	Tips used:	Gilson D200
Z Factor:	1.0031µL/mg	Cust Order:	SH462154-0
Humidity:	47.0%	Cust Ref:	SARAH ROBERTS
		End User:	

CALIBRATION DETAILS

Vol./Spec Code	50.000	(G13)	200.000	(G15)
Weighing 1 (mg)	49.900	(pass)	199.960	(pass)
Weighing 2 (mg)	49.970	(pass)	199.870	(pass)
Weighing 3 (mg)	49.960	(pass)	199.900	(pass)
Weighing 4 (mg)	49.980	(pass)	199.900	(pass)
Mean Wgt (mg)	49.952		199.908	
Mean Vol (µL)	50.107	(pass)	200.527	(pass)
Abs Inacc. (µL)	0.107	(pass)	0.527	(pass)
Rel Inacc. (%)	0.214	(pass)	0.263	(pass)
Abs SD (µL)	0.036	(pass)	0.038	(pass)
CV%	0.072	(pass)	0.019	(pass)
OVERALL STATUS		PASS		PASS

SERVICING DETAILS

NO SPARE PARTS USED

Technicians Signature .....

17 JUL 2003

Warranty Expiry Date .....

Specification Information:	Spec Code	Min Vol (µL)	Max Vol (µL)	Abs SD (µL)	CV%
	G13	49.5	50.5	<= 0.200	<= 0.400
	G15	198.4	201.6	<= 0.300	<= 0.150

Values Exclude Environmental Adjustment

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Regd. Office: 20 Charles Street, Luton, Bedfordshire LU2 0EB Registration N°: 974301 England V.A.T. Registration N°: 196 2842 29

The calibration check was carried out using the gravimetric method as stipulated by the manufacturer, with weights that are traceable to the National Physical Laboratory.

LIQUID HANDLING

FS 26081

ANACHEM

Anachem Ltd. Anachem House, Charles Street, Luton, Bedfordshire, LU2 0EB, U.K.

Date Printed: 06-Dec-2002

CALIBRATION

ANACHEM CALL NUMBER: 108120

ORDER DETAILS

Calibration Date: 06-Dec-2002
Account/Customer: 02009 UNIVERSITY OF BATH

Contact: UNIVERSITY OF BATH

Ave Room Temp: 21.0 deg.C
Ave Water Temp: 21.0 deg.C
Technician: Liquid Handling Dept
Air Pressure: 1009hPa
Z Factor: 1.0031µL/mg
Humidity: 46.0%

PIPETTE DETAILS

Model: P1000

Serial No: T53730K

Thermometer: TH13
Barometer: AB1
Balance: J
Balance Ref: J31974
Tips used: Gilson D1000
Cust Order: SH 461739-
Cust Ref: SARAH ROBERTS
End User:

CALIBRATION DETAILS

Vol./Spec Code	200.000	(G16)	1000.000	(G18)
Weighing 1 (mg)	199.430	(pass)	996.130	(pass)
Weighing 2 (mg)	198.670	(pass)	994.300	(pass)
Weighing 3 (mg)	199.050	(pass)	995.850	(pass)
Weighing 4 (mg)	198.740	(pass)	995.690	(pass)
Mean Wgt (mg)	198.973		995.493	
Mean Vol (µL)	199.589	(pass)	998.579	(pass)
Abs Inacc. (µL)	-0.411	(pass)	-1.421	(pass)
Rel Inacc. (%)	-0.206	(pass)	-0.142	(pass)
Abs SD (µL)	0.348	(pass)	0.818	(pass)
CV%	0.174	(pass)	0.082	(pass)
OVERALL STATUS		PASS		PASS

SERVICING DETAILS

Spares Code		Qty Used
PISTON	H23847	1

6 MONTH SERVICE WARRANTY

Technicians Signature .....

Warranty Expiry Date 06 JUN 2003

Specification Information:	Spec Code	Min Vol (µL)	Max Vol (µL)	Abs SD (µL)	CV%
	G16	197	203	<= 0.600	<= 0.300
	G18	992	1008	<= 1.500	<= 0.150

Values Exclude Environmental Adjustment

Produced from computerised Liquid Handling System - (C) Anachem Ltd 1998 V6.1g

Telephone: +44 (0)1582 745061 Fax: +44 (0)1582 745130 www.anachem.co.uk email: lhlab@anachem.co.uk

Regd. Office: 20 Charles Street, Luton, Bedfordshire LU2 0EB Registration N°: 974301 England V.A.T. Registration N°: 196 2842 29

The calibration check was carried out using the gravimetric method as stipulated by the manufacturer, with weights that are traceable to the National Physical Laboratory.

LIQUID HANDLING

FS 26081

APPENDIX 11:

Presentation of results at conferences and educational meetings

Results obtained during the course of this research project have been presented at the following conferences and educational meetings:

BAPEN, Harrogate, November 2000: Annual Meeting of the British Association for Parenteral and Enteral Nutrition. Results from the literature were presented orally and as a poster.

BAPEN, Harrogate, November 2001: Annual Meeting of the British Association for Parenteral and Enteral Nutrition. Results from the survey were presented orally and as a poster. The abstract was also published in the Proceedings of the Nutrition Society, Volume 61, Supplement 11A (Appendix 11)

Nutriforum, Bristol, May 2002: Clinical and Practical Choices for the Future (Chair: Dr. John Puntis) Educational meeting approved by the College of Pharmacy Practice and all medical Royal Colleges.

BPC, Manchester, September 2002: Results from the survey were presented as a poster. The abstract was also published in the International Journal of Pharmacy Practice, Supplement: Pharmacy Practice Research, R77 (Appendix 11)

Nutriforum, Leeds, March 2003: Clinical Nutrition. You Have a Choice (Chair: Mr. John McFie) Educational meeting approved by the College of Pharmacy Practice and all medical Royal Colleges.

APPENDIX 12:

Manuscripts submitted for publication

The following manuscripts have been submitted for publication:

B U Klüttgens, G J Sewell, and A J Nunn: Current clinical practice in neonatal and pediatric parenteral nutrition in Europe. *Journal of European Hospital Pharmacy*

B U Klüttgens, A J Nunn, and G J Sewell: Standardized Neonatal and Pediatric Parenteral Nutrition in Europe. *Clinical Nutrition*

B U Klüttgens, G J Sewell, A J Nunn, and A Le Brun: Retrospective observational study of parenteral nutrition prescribing for infants. *Archives of Diseases in Childhood (Fetal and Neonatal Edition)*

APPENDIX 13:

Published abstracts: BAPEN 2000, BAPEN 2001, BPC 2002

Literature comparison of basic parenteral nutrition solutions for neonates, is standardisation possible? By B.U. KLUETTGENS [1], G.J. SEWELL [1] and A.J. NUNN [2], [1] *University of Bath, Bath BA2 7AY and* [2] *Alder Hey Royal Liverpool Children's NHS Trust Liverpool L12 2AP*

Commercial complete parenteral nutrition solutions are not available for neonates. Therefore, nutritional solutions have to be compounded in hospital pharmacies. In order to increase safety and reduce cost, hospitals may introduce standard feeding regimens (Digel, 1998). The literature has been searched, using EMBASE, The Web of Science, and Medline, for publications about standardised nutrition for the neonatal patient group. Data has been retrieved from England, Spain, and Germany. Discussions with collegues have revealed that several other centers use standardised parenteral nutrition for neonates, but have not published their results.

Standardisation of parenteral nutrition for neonates may involve the preparation of a single formula where the volume infused is altered according to the patient's weight. This is only applicable for stable patients without special requirements since if a different quantity of any one volume is required, then the amount of all others is also altered. In a recent article, is has been estimated that up to two third of neonates could be given a range of pre-compounded standard solutions (Beecroft *et al*, 1999).

The most recent data available on standardised regimens is listed below. In San Sebastian, Spain, a concentrate is manufactured, which can be diluted according to the patients needs (Aldamiz-Echevrria *et al*, 1995). The comparison shows that individually developed regimens in different European countries do not differ substantially.

Requirements per kg in 24hrs	Plymouth, UK (Unpublished data)	Essen, Germany	Heilbronn, Germany (Willimsky *et al*, 2000)	San Sebastian, Spain
Volume	150	150	150	150
Glucose	14	15	15	10
Nitrogen	0.3	0.38	0.38	0.32
Sodium	-	4.5	4.5	4.0
Potassium	-	2.0	3.0	2.5
Calcium	-	1.5	1.5	1.2
Magnesium	-	0.2	0.17	0.28
Phosphate	-	1.5	1.5	1.0
Chloride	-	3.5	4.5	4.0

Standardising parenteral nutrition and producing the solutions in batches makes more extensive quality assurance possible and commercial manufacture practicable, and therefore increases the safety of this treatment. A high quality and safe parenteral nutrition is especially important in these most susceptible patients. The reviewed data supports suggestions that a wide-ranging standardisation of neonatal parenteral nutrition is feasible.

Future directions of this study include a questionnaire directed at key European centres aiming to evaluate the practice of supplying parenteral nutrition to paediatric patients, the development of standard regimens, and stability studies on a standardised regimen, including peroxide formation.

Aldamiz-Echevarria L, Bachiller Cacho MP, Gayan Lere MJ, Paisan Grisolia L, Lopez Arzoz, Barcia Romero MJ & Albisu Andrade Y (1995) *Anales espanoles de pediatria* **43 (3)**, 203-207

Beecroft C, Martin H & Puntis JWL (1999) *Clincial Nutrition* **18 (2)**, 83-85

Digel S (1998) *Krankenhauspharmazie* **19 (2)**, 62-65

Willimsky S, Kilian R, Geier N, Schwartz M, Runge H & Kachel W (2000) *Monatsschrift fur Kinderheilkunde* **148**, 713-718

European survey of current practice in the delivery of parenteral nutrition to neonates and children. By B.U. KLŰTTGENS [1], G.J. SEWELL [1] and A.J. NUNN [2], [1] *University of Bath, Bath BA2 7AY and* [2] *Alder Hey Royal Liverpool Children's NHS Trust, Liverpool L12 2AP*

As part of a project to determine whether standard parenteral nutrition admixtures could be used more widely in neonatal and paediatric practice a survey has been undertaken in five European countries, including Spain, Italy, France, Germany and the UK. The objective was to characterize current practice in the provision of parenteral nutrition for neonates and children. A total of 90 hospitals were included in this study, covering nearly 10,000 pediatric beds.

The survey was undertaken in the form of a postal questionnaire aimed at clinicians and pharmacists.

In order to define the delivery of parenteral nutrition the following issues have been addressed:

- Where are the parenteral nutrition solutions compounded?
- Is fat infused separately or as All-in-One mixtures?
- When are vitamins and trace metals commenced?
- Are filters and light protection used during drug administration?
- Is any form of standard admixture used?

Results show that in some issues the five countries differ considerably: In the UK 90% of hospitals have a compounding unit for parenteral nutrition, in Germany and Italy parenteral nutrition is still regularly compounded on wards with only a third of hospitals providing a pharmacy compounding unit. In France and Spain commercial manufacturers often provide the compounding service, with only half of the hospitals providing a pharmacy-based service.

The lipid emulsion is usually given as a separate infusion to neonates (81%) and to most children (51%).

Vitamins and trace metals are usually given from day one for seven days per week. A minority of hospitals only include the micronutrients 3-4 days a week and some start the supply seven days after starting parenteral nutrition support.

Filters are used in 54% of hospitals. The parenteral nutrition bag is frequently protected form light (47%), but the use of light protecting tubing is less common (14%).

Despite the lack of international recommendations regarding the use of standard formulations, 43% of hospitals have indicated that they have introduced some kind of standard bag. The reasons for the introductions of standardized bags are: Convenience (24%), capacity problems regarding the compounding of individual bags (19%) and increased safety with the use of standard bags (11%).

29% of respondents have indicated that they would not be prepared to introduce standard regimens for their neonates and children.

The practice of parenteral nutrition delivery varies considerable throughout Europe. Although little is published on the use of standardized parenteral nutrition, many have introduced standard regimens and there continues to be a lively discussion regarding this issue.

Further work is required to explore the different European practices and to establish whether tailored or standard regimens provide better nutritional intake.

Current paediatric parenteral nutrition practice in Europe

B.U. Kluettgens [1], G.J. Sewell [1] and A.J. Nunn [2]
[1] *University of Bath, Bath BA2 7AY and* [2] *Alder Hey Royal Liverpool Children's NHS Trust, Liverpool L12 2AP*

Introduction
Parenteral nutrition for neonates and children is highly complex and involves many health-care professionals. Little is known about the clinical and pharmaceutical practice of paediatric parenteral nutrition in different European countries.

Objectives
The aim of this survey was to identify similarities and differences in the way parenteral nutrition is prescribed, compounded and administered in five European countries (France, Germany, Italy, Spain, and the UK).

Method
A postal questionnaire survey was undertaken, addressing 218 hospitals. Hospitals where selected with the help of personal contacts in each country. Questions were asked regarding prescribing practice, compounding facilities, involvement of different health-care professionals, use of filters, and use of standardized, pre-compounded formulae.

Results
The overall response rate was 45% (France 45%; Germany 44%; Italy 29%; Spain 36%; UK 71%). Prescribing of parenteral nutrition is usually carried out by clinicians (80%), although sometimes Pharmacists prescribe (6%). Special compounding facilities are present in most UK (87%) and Spanish hospitals (64%), but less often in Germany (35%), France (40%), and Italy (50%).

Table 1 shows the extent of the use of filters and light protection overall

	Yes, always	Yes, sometimes	No
Use of Filter (N=98)	57 %	16 %	27 %
Light protection (bag) (N=97)	48 %	24 %	28 %
Light protection (tubing) (N=92)	15 %	24 %	61 %

The lipid emulsion is usually given as a separate infusion to neonates (81%) and to most children (51%). Vitamins and trace metals are typically given from the first day of parenteral nutrition for seven days per week. A minority of hospitals only include the micronutrients 3-4 days a week and some start the supply seven days after starting parenteral nutrition support.
Standardized, pre-compounded nutrition formulae are used in 43% of hospitals. These include commercially available solutions, externally produced solutions to internal specification, or in-house manufactured solutions.

Discussion
Differences in clinical and pharmaceutical practice in the five European countries are mainly related to the involvement of different professionals. This is probably related to cultural differences and different roles of clinician, pharmacists, and nurses. In Germany, Pharmacists are only rarely involved in the compounding of parenteral nutrition, and in France external suppliers are used. Other elements of parenteral nutrition support show widespread similarities between the study countries.
Although little is published about the use of standardized parenteral nutrition, many neonatal and paediatric centres have introduced standard regimens and there is currently considerable interest in this issue [1]. Standardising parenteral nutrition and producing the solutions in batches makes more extensive quality assurance possible and commercial manufacture practicable, and therefore increases the safety of this treatment. The compounding process becomes less time consuming and more economic.
Further work is needed to investigate the nutritional adequacy and safety of standardized parenteral nutrition.

1. Beecroft C, Martin H, Puntis JWL. How often do parenteral nutrition prescriptions for the newborn need to be individualized? Clinical Nutrition 1999;18(2):83-85.